PATIENT INFORMATION LEAFLET
For the use of a Registered Medical Practitioner, or a hospital, or a Laboratory only.

DAPAGLIFLOZIN 10 MG & METFORMIN HYDROCHLORIDE (ER) 500 MG TABLETS

DAPAGLIPLEX™ MXR 10/500

1. Generic Name
Dapagliflozin 10 mg & Metformin Hydrochloride (ER) 500 mg Tablets
2. Qualitative and Quantitative Composition
Each film coated tablet contains:

Dapagliflozin Propanediol USP	
Eq. to Dapagliflozin	10 mg
Metformin Hydrochloride IP	500 mg
(As Extended Release)	

Colours: Ferric Oxide Yellow USP-NF & Titanium Dioxide IP

3. Dosage form and strength
Oral dosage form (Tablet)
Dapagliflozin 10 mg & Metformin Hydrochloride (ER) 500 mg Tablets

4. Clinical particulars
4.1 Therapeutic indication
It 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.

4.2 Posology and method of administration
Adults with normal renal function (glomerular filtration rate [GFR] ≥ 90 mL/min)
The recommended dose is one tablet twice daily. Each tablet contains a fixed dose of dapagliflozin and metformin.

For patients insufficiently controlled on metformin monotherapy or metformin in combination with other medicinal products for the treatment of diabetes
Patients insufficiently controlled on metformin alone or in combination with other medicinal products for the treatment of diabetes should receive a total daily dose of Dapagliflozin & Metformin Hydrochloride (ER) Tablets equivalent to dapagliflozin 10 mg, plus the total daily dose of metformin, or the nearest therapeutically appropriate dose, already being taken. When Dapagliflozin & Metformin Hydrochloride (ER) Tablets is used in combination with insulin or an insulin secretagogue such as sulphonylurea, a lower dose of insulin or sulphonylurea may be considered to reduce the risk of hypoglycaemia.

For patients switching from separate tablets of dapagliflozin and metformin
Patients switching from separate tablets of dapagliflozin (10 mg total daily dose) and metformin to Dapagliflozin & Metformin Hydrochloride (ER) Tablets should receive the same daily dose of dapagliflozin and metformin already being taken or the nearest therapeutically appropriate dose of metformin.

Special populations
Renal impairment
A GFR should be assessed before initiation of treatment with Metformin containing medicinal products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.
The maximum daily dose of Metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of Metformin in patients with GFR < 60 mL/min.
If no adequate strength of Dapagliflozin & Metformin Hydrochloride (ER) Tablets is available, individual mono-components should be used instead of the fixed dose combination.

Table 1. Dosage in patients with renal impairment

GFR mL/min	Metformin	Dapagliflozin
60-89	Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function.	Maximum total daily dose is 10 mg.
45-59	Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.	Dapagliflozin should not be initiated. Maximum total daily dose is 10 mg.
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	Dapagliflozin is not recommended.
< 30	Metformin is contraindicated.	Dapagliflozin is not recommended.

Hepatic impairment
This medicinal product must not be used in patients with hepatic impairment.
***Elderly* (≥ 65 years)**
Because Metformin is eliminated in part by the kidney, and because elderly patients are more likely to have decreased renal function, this medicinal product should be used with caution as age increases. Monitoring of renal function is necessary to aid in prevention of Metformin-associated lactic acidosis, particularly in elderly patients. Risk of volume depletion with Dapagliflozin should also be taken into account.
Paediatric population
The safety and efficacy of Dapagliflozin & Metformin Hydrochloride (ER) Tablets in children and adolescents aged 0 to < 18 years have not yet been established. No data are available.
Method of administration
Dapagliflozin & Metformin Hydrochloride (ER) Tablets should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin.

4.3 Contraindications
Dapagliflozin & Metformin Hydrochloride (ER) Tablets is contraindicated in patients with:
- hypersensitivity to the active substances or to any of the excipients, any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis),
- diabetic pre-coma,
- severe renal failure (GFR < 30 mL/min),
- acute conditions with the potential to alter renal function such as:
  - dehydration,
  - severe infection,
  - shock;
- acute or chronic disease which may cause tissue hypoxia such as:
  - cardiac or respiratory failure,
  - recent myocardial infarction,
  - shock;
- hepatic impairment,
- acute alcohol intoxication, alcoholism.

4.4 Special warnings and precautions for use
Lactic Acidosis
There have been post-marketing cases of Metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis.
Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/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 & Metformin Hydrochloride (ER) Tablets.
In Dapagliflozin & Metformin Hydrochloride (ER) Tablets 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 & Metformin Hydrochloride (ER) Tablets and report these symptoms to their healthcare provider.
For each of the known and possible risk factors for Metformin-associated lactic acidosis, recommendations to reduce the risk of and manage Metformin-associated lactic acidosis are provided below:

Renal Impairment: The postmarketing Metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of Metformin accumulation and Metformin-associated lactic acidosis increases with the severity of renal impairment because Metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include:
- Before initiating Dapagliflozin & Metformin Hydrochloride (ER) Tablets, obtain an estimated glomerular filtration rate (eGFR).
- Dapagliflozin & Metformin Hydrochloride (ER) Tablets is contraindicated in patients with an eGFR less than 60 mL/minute/1.73 m^2.
- Obtain an eGFR at least annually in all patients taking Dapagliflozin & Metformin Hydrochloride (ER) Tablets. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

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

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

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

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

Hypoxic States: Several of the postmarketing cases of Metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue Dapagliflozin & Metformin Hydrochloride (ER) Tablets.
Excessive Alcohol Intake: Alcohol potentiates the effect of Metformin on lactate metabolism and this may increase the risk of Metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving Dapagliflozin & Metformin Hydrochloride (ER) Tablets.

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

Hypotension
Dapagliflozin causes intravascular volume contraction. Symptomatic hypotension can occur after initiating Dapagliflozin, particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics.
Before initiating Dapagliflozin & Metformin Hydrochloride (ER) Tablets in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms of hypotension after initiating therapy.

Ketoacidosis
Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing 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 & Metformin Hydrochloride (ER) Tablets is not indicated for the treatment of patients with Type 1 Diabetes Mellitus.

Patients treated with Dapagliflozin & Metformin Hydrochloride (ER) Tablets who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of blood glucose levels as ketoacidosis associated with Dapagliflozin & Metformin Hydrochloride (ER) Tablets may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, Dapagliflozin & Metformin Hydrochloride (ER) Tablets should be discontinued, the patient should be evaluated and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with Type 1 Diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases,
factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake due to illness or surgery, pancreatic disorders suggesting insulin deficiency (e.g., Type 1 Diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating Dapagliflozin & Metformin Hydrochloride (ER) Tablets, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction and alcohol abuse. In patients treated with Dapagliflozin & Metformin Hydrochloride (ER) Tablets consider monitoring for ketoacidosis and temporarily discontinuing Dapagliflozin & Metformin Hydrochloride (ER) Tablets in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

Acute Kidney Injury and Impairment in Renal Function
Dapagliflozin causes intravascular volume contraction and can cause renal impairment. There have been postmarketing 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 & Metformin Hydrochloride (ER) Tablets, 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 & Metformin Hydrochloride (ER) Tablets 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 & Metformin Hydrochloride (ER) Tablets promptly and institute treatment.

Dapagliflozin increases serum creatinine and decreases eGFR. Elderly patients and patients with impaired renal function may be more susceptible to these changes. Adverse reactions related to renal function can occur after initiating Dapagliflozin & Metformin Hydrochloride (ER) Tablets. Renal function should be evaluated prior to initiation of Dapagliflozin & Metformin Hydrochloride (ER) Tablets and monitored periodically thereafter. Dapagliflozin & Metformin Hydrochloride (ER) Tablets is contraindicated in patients with an eGFR below 60 mL/min/1.73 m^2.

Urosepsis and Pyelonephritis
There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including Dapagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Fournier's gangrene
Cases of a rare but serious infection of the genitals and area around the genitals have been reported with this class of type 2 diabetes medicines i.e., Sodium Glucose Cotransporter-2 (SGLT-2) inhibitors. This serious rare infection, called necrotizing fasciitis of the perineum, is also referred to as Fournier's gangrene.

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 & Metformin Hydrochloride (ER) Tablets.

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 & Metformin Hydrochloride (ER) Tablets 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 & Metformin Hydrochloride (ER) Tablets.

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 hematuria (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 & Metformin Hydrochloride (ER) Tablets 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 & Metformin Hydrochloride (ER) Tablets should be considered.

Macrovascular Outcomes
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Dapagliflozin & Metformin Hydrochloride (ER) Tablets.

4.5 Drug interactions
Positive Urine Glucose Test
Dapagliflozin
Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

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

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

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

Alcohol
Alcohol is known to potentiate the effect of Metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving Dapagliflozin & Metformin Hydrochloride (ER) Tablets.

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 & Metformin Hydrochloride (ER) Tablets, the patient should be observed closely for loss of glycemic control. When such drugs are withdrawn from a patient receiving Dapagliflozin & Metformin Hydrochloride (ER) Tablets, 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.

4.6 Use in special population (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)
1. Pregnancy
Pregnancy Category C
There are no adequate and well-controlled studies of Dapagliflozin & Metformin Hydrochloride (ER) Tablets or its individual components in pregnant women. Based on results of reproductive and developmental toxicity studies in animals, Dapagliflozin, a component of Dapagliflozin & Metformin Hydrochloride (ER) Tablets, may affect renal development and maturation. In a juvenile rat study, increased incidence and/or severity of renal pelvic and tubular dilatations were evident at the lowest tested dose which was approximately 15 times clinical exposure from a 10 mg dose.
These outcomes occurred with drug exposures during periods of animal development that correlate with the late second and third trimesters of human pregnancy. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. Dapagliflozin & Metformin Hydrochloride (ER) Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Dapagliflozin
In a juvenile toxicity study, when Dapagliflozin was dosed directly to young rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg/kg/day, increased kidney weights and renal pelvic and tubular dilatations were reported at all levels. Exposure at the lowest tested dose was 15 times the maximum clinical dose, based on AUC. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1-month recovery period. In a prenatal and postnatal development study, maternal rats were dosed from gestation day 6 through lactation day 21 at doses of 1, 15, or 75 mg/kg/day, and pups were indirectly exposed in utero and throughout lactation. Increased incidence or severity of renal pelvic dilatation was observed in adult offspring of treated dams at 75 mg/kg/day (maternal and pup Dapagliflozin exposures were 1415 times and 137 times, respectively, the human values at the clinical dose). Dose-related reductions in pup body weights were observed at doses ≥1 mg/kg/day (approximately ≥19 times the clinical dose). No adverse effects on developmental endpoints were noted at 1 mg/kg/day, or approximately 19 times the clinical dose.
In embryo-fetal development studies in rats and rabbits, Dapagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. No developmental toxicities were observed in rabbits at any dose tested. In rats, Dapagliflozin was neither embryo lethal nor teratogenic at doses up to 75 mg/kg/day or 1441 times the maximum clinical dose of 10 mg. At higher doses in rats, malformations of blood vessels, ribs, vertebrae, manubria, and skeletal variations in fetuses at ≥150 mg/kg or 2344 times the 10 mg clinical dose were observed.

Metformin Hydrochloride
Metformin Hydrochloride did not cause adverse developmental effect when administered to pregnant Sprague Dawley rats and rabbits up to 600 mg/kg/day during the period of organogenesis. This represents an exposure of about 2- and 6-times a 2000 mg clinical dose based on body surface area (mg/m^2) for rats and rabbits, respectively. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the MRHD of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to Metformin.

2. Nursing Mothers
It is not known whether Dapagliflozin & Metformin Hydrochloride (ER) Tablets is excreted in human milk. In studies performed with the individual components, both Dapagliflozin (reaching levels 0.49 times that found in maternal plasma) and Metformin are excreted in the milk of lactating rats.
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 & Metformin Hydrochloride (ER) Tablets, taking into account the importance of the drug to the mother.

3. Pediatric Use
Safety and effectiveness of Dapagliflozin & Metformin Hydrochloride (ER) Tablets in pediatric patients under 18 years of age have not been established.

4. Geriatric Use
No Dapagliflozin & Metformin Hydrochloride (ER) Tablets dosage change is recommended based on age. More frequent assessment of renal function is recommended in elderly patients.

Dapagliflozin
A total of 1424 (24%) of the 5936 Dapagliflozin-treated patients were 65 years and over and 207 (3.5%) patients were 75 years and older in a pool of 21 double-blind, controlled, clinical safety and efficacy studies of Dapagliflozin. After controlling for level of renal function (eGFR), efficacy was similar for patients under age 65 years and those 65 years and older. In patients ≥65 years of age, a higher proportion of patients treated with Dapagliflozin had adverse reactions related to volume depletion and renal impairment or failure compared to patients treated with placebo.

Metformin Hydrochloride
Controlled clinical studies of Metformin did not include sufficient numbers of elderly patients to determine whether they respond differently than younger patients, although other reported clinical experience has not identified differences in responses between the elderly and young patients. Metformin is known to be substantially excreted by the kidney and because the risk of lactic acidosis with Metformin is greater in patients with moderately to severely impaired renal function. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients.
5. Patients with Mild Renal Impairment (eGFR ≥60 to <90 mL/min/1.73 m^2)
Dapagliflozin
The pool of 21 double-blind, active- and placebo-controlled clinical safety and efficacy studies (Dapagliflozin as monotherapy or in combination with other antidiabetic therapies) included 53% (4906/9339) of patients with mild renal impairment. The safety profile in patients with mild renal impairment is similar to that in the overall population.

6. Hepatic Impairment
Use of Metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Dapagliflozin & Metformin Hydrochloride (ER) Tablets is not recommended in patients with hepatic impairment.

4.7 Effects on ability to drive and use machines
Dapagliflozin & Metformin Hydrochloride (ER) Tablets has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when this medicinal product is used in combination with other glucose-lowering medicinal products known to cause hypoglycaemia.

4.8 Undesirable effects
Dapagliflozin & Metformin Hydrochloride (ER) Tablets has been demonstrated to be bioequivalent with coadministered dapagliflozin and metformin. There have been no therapeutic clinical trials conducted with Dapagliflozin & Metformin Hydrochloride (ER) Tablets.

Dapagliflozin plus Metformin
Summary of the safety profile
In an analysis of 5 placebo-controlled dapagliflozin add-on to metformin studies, the safety results were similar to that of the pre-specified pooled analysis of 13 placebo-controlled dapagliflozin studies. No additional adverse reactions were identified for the dapagliflozin plus metformin group compared with those reported for the individual components. In the separate dapagliflozin add-on to metformin pooled analysis, 623 subjects were treated with dapagliflozin 10 mg as add-on to metformin and 523 were treated with placebo plus metformin.

Dapagliflozin
Summary of the safety profile
In the clinical studies in type 2 diabetes, more than 15,000 patients have been treated with dapagliflozin.
The primary assessment of safety and tolerability was conducted in a pre-specified pooled analysis of 13 short-term (up to 24 weeks) placebo-controlled studies with 2,360 subjects treated with dapagliflozin 10 mg and 2,295 treated with placebo.
In the dapagliflozin cardiovascular outcomes study 8,574 patients received dapagliflozin 10 mg and 8,569 received placebo for a median exposure time of 48 months. In total, there were 30,623 patient-years of exposure to dapagliflozin.
The most frequently reported adverse reactions across the clinical studies were genital infections.

Tabulated list of adverse reactions
The following adverse reactions have been identified in the placebo-controlled dapagliflozin plus metformin clinical studies, dapagliflozin clinical studies and metformin clinical studies and post-marketing experience. None were found to be dose-related. Adverse reactions listed below are classified according to frequency and system organ class. Frequency categories are defined according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from the available data).
Table 2. Adverse reactions in dapagliflozin and metformin immediate-release clinical trial and post-marketing data[a]

System organ class	Very common	Common	Uncommon	Rare	Very rare
Infections and infestations		Vulvovaginitis, balanitis and related genital infections[*,b,c] Urinary tract infection[*,b,d]	Fungal infection[**]		Necrotising fasciitis of the perineum (Fournier's gangrene)[b,k]
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin)[b]		Volume depletion[b,e] Thirst[**]	Diabetic ketoacidosis[b,k,l]	Lactic acidosis Vitamin B12 deficiency[b,§]
Nervous system disorders		Taste disturbance[§] Dizziness			
Gastrointestinal disorders	Gastrointestinal symptoms[i,§]		Constipation[**] Dry mouth[**]		
Hepatobiliary disorders					Liver function disorders[§] Hepatitis[§]
Skin and subcutaneous tissue disorders		Rash[m]			Urticaria[§] Erythema[§] Pruritus[§]
Musculoskeletal and connective tissue disorders		Back pain[*]			
Renal and urinary disorders		Dysuria Polyuria[*,f]	Nocturia[**]		
Reproductive system and breast disorders			Vulvovaginal pruritus[**] Pruritus genital[**]		
Investigations		Haematocrit increased[g] Creatinine renal clearance decreased during initial treatment[b] Dyslipidaemia[i]	Blood creatinine increased during initial treatment[**,a] Blood urea increased[**] Weight decreased[**]		

[a] The table shows adverse reactions identified from up to 24-week (short-term) data regardless of glycaemic rescue, except those marked with §, for which adverse reaction and frequency categories are based on information from the metformin Summary of Product Characteristics available in the European Union.
[b] See corresponding subsection below for additional information.
[c] Vulvovaginitis, balanitis and related genital infections includes, e.g. the predefined preferred terms: vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, vulval abscess.
[d] Urinary tract infection includes the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection and prostatitis.
[e] Volume depletion includes, e.g. the predefined preferred terms: dehydration, hypovolaemia, hypotension.
[f] Polyuria includes the preferred terms: pollakiuria, polyuria, urine output increased.
[g] Mean changes from baseline in haematocrit were 2.30% for dapagliflozin 10 mg versus –0.33% for placebo. Haematocrit values >55% were reported in 1.3% of the subjects treated with dapagliflozin 10 mg versus 0.4% of placebo subjects.
[h] Long-term treatment with metformin has been associated with a decrease in vitamin B12 absorption which may very rarely result in clinically significant vitamin

B12 deficiency (e.g. megaloblastic anaemia).
[i] Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases.
[j] Mean percent change from baseline for dapagliflozin 10 mg versus placebo, respectively, was: total cholesterol 2.5% versus 0.0%; HDL cholesterol 6.0% versus 2.7%; LDL cholesterol 2.9% versus -1.0%; triglycerides -2.7% versus -0.7%.
[k] See section 4.4.
[l] Reported in the cardiovascular outcomes study in patients with type 2 diabetes. Frequency is based on annual rate.
[m] Adverse reaction was identified through post-marketing surveillance with the use of dapagliflozin. Rash includes the following preferred terms, listed in order of frequency in clinical trials: rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, and rash erythematous. In active- and placebo-controlled clinical trials (dapagliflozin, N=5936, All control, N=3403), the frequency of rash was similar for dapagliflozin (1.4%) and all control (1.4%), respectively.
[*] Reported in ≥ 2% of subjects and ≥ 1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.
[**] Reported by the investigator as possibly related, probably related or related to study treatment and reported in ≥ 0.2% of subjects and ≥ 0.1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

Description of selected adverse reactions

Dapagliflozin plus Metformin

Hypoglycaemia

In studies with dapagliflozin in add-on combination with metformin, minor episodes of hypoglycaemia were reported at similar frequencies in the group treated with dapagliflozin 10 mg plus metformin (6.9%) and in the placebo plus metformin group (5.5%). No major events of hypoglycaemia were reported. Similar observations were made for the combination of dapagliflozin with metformin in drug-naïve patients.
In an add-on to metformin and a sulphonylurea study, up to 24 weeks, minor episodes of hypoglycaemia were reported in 12.8% of subjects who received dapagliflozin 10 mg plus metformin and a sulphonylurea and in 3.7% of subjects who received placebo plus metformin and a sulphonylurea. No major events of hypoglycaemia were reported.

Dapagliflozin

Vulvovaginitis, balanitis and related genital infections

In the 13-study safety pool, vulvovaginitis, balanitis and related genital infections were reported in 5.5% and 0.6% of subjects who received dapagliflozin 10 mg and placebo, respectively. Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females (8.4% and 1.2% for dapagliflozin and placebo, respectively), and subjects with a prior history were more likely to have a recurrent infection.
In the dapagliflozin cardiovascular outcomes study, the number of patients with serious adverse events of genital infections were few and balanced: 2 patients in each of the dapagliflozin and placebo groups.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Cases of Fournier's gangrene have been reported postmarketing in patients taking SGLT2 inhibitors, including dapagliflozin.
In the dapagliflozin cardiovascular outcomes study with 17,160 type 2 diabetes mellitus patients and a median exposure time of 48 months, a total of 6 cases of Fournier's gangrene were reported, one in the dapagliflozin-treated group and 5 in the placebo group.

Hypoglycaemia

The frequency of hypoglycaemia depended on the type of background therapy used in each study.
For studies of dapagliflozin as add-on to metformin or as add-on to sitagliptin (with or without metformin), the frequency of minor episodes of hypoglycaemia was similar (< 5%) between treatment groups, including placebo up to 102 weeks of treatment. Across all studies, major events of hypoglycaemia were uncommon and comparable between the groups treated with dapagliflozin or placebo. In a study with add-on insulin therapy, higher rates of hypoglycaemia were observed.
In an add-on to insulin study up to 104 weeks, episodes of major hypoglycaemia were reported in 0.5% and 1.0% of subjects in dapagliflozin 10 mg plus insulin at Weeks 24 and 104, respectively, and in 0.5% of subjects treated with placebo plus insulin groups at Weeks 24 and 104. At Weeks 24 and 104, minor episodes of hypoglycaemia were reported, respectively, in 40.3% and 53.1% of subjects who received dapagliflozin 10 mg plus insulin and in 34.0% and 41.6% of the subjects who received placebo plus insulin.
In the dapagliflozin cardiovascular outcomes study, no increased risk of major hypoglycaemia was observed with dapagliflozin therapy compared with placebo. Major events of hypoglycaemia were reported in 58 (0.7%) patients treated with dapagliflozin and 83 (1.0%) patients treated with placebo.

Volume depletion

In the 13-study safety pool, reactions suggestive of volume depletion (including, reports of dehydration, hypovolaemia or hypotension) were reported in 1.1% and 0.7% of subjects who received dapagliflozin 10 mg and placebo, respectively; serious reactions occurred in < 0.2% of subjects balanced between dapagliflozin 10 mg and placebo.
In the dapagliflozin cardiovascular outcomes study, the numbers of patients with events suggestive of volume depletion were balanced between treatment groups: 213 (2.5%) and 207 (2.4%) in the dapagliflozin and placebo groups, respectively. Serious adverse events were reported in 81 (0.9%) and 70 (0.8%) in the dapagliflozin and placebo group, respectively. Events were generally balanced between treatment groups across subgroups of age, diuretic use, blood pressure and ACE-I/ARB use. In patients with eGFR < 60 mL/min/1.73 m^2 at baseline, there were 19 events of serious adverse events suggestive of volume depletion in the dapagliflozin group and 13 events in the placebo group.

Diabetic ketoacidosis

In the dapagliflozin cardiovascular outcomes study, with a median exposure time of 48 months, events of DKA were reported in 27 patients in the dapagliflozin 10 mg group and 12 patients in the placebo group. The events occurred evenly distributed over the study period. Of the 27 patients with DKA events in the dapagliflozin group, 22 had concomitant insulin treatment at the time of the event. Precipitating factors for DKA were as expected in a type 2 diabetes mellitus population.

Urinary tract infections

In the 13-study safety pool, urinary tract infections were more frequently reported for dapagliflozin compared with placebo (4.7% versus 3.5%, respectively; see section 4.4). Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females, and subjects with a prior history were more likely to have a recurrent infection.
In the dapagliflozin cardiovascular outcomes study, serious events of urinary tract infections were reported less frequently for dapagliflozin 10 mg compared with placebo, 79 (0.9%) events versus 109 (1.3%) events, respectively.

Increased creatinine

Adverse reactions related to increased creatinine were grouped (e.g. decreased renal creatinine clearance, renal impairment, increased blood creatinine and decreased glomerular filtration rate). This grouping of reactions was reported in 3.2% and 1.8% of patients who received dapagliflozin 10 mg and placebo, respectively. In patients with normal renal function or mild renal impairment (baseline eGFR ≥ 60 mL/min/1.73m^2) this grouping of reactions were reported in 1.3% and 0.8% of patients who received dapagliflozin 10 mg and placebo, respectively. These reactions were more common in patients with baseline eGFR ≥ 30 and < 60 mL/min/1.73m^2 (18.5% dapagliflozin 10 mg vs 9.3% placebo).
Further evaluation of patients who had renal-related adverse events showed that most had serum creatinine changes of ≤ 0.5 mg/dL from baseline. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment.
In the dapagliflozin cardiovascular outcomes study, including elderly patients and patients with renal impairment (eGFR less than 60 mL/min/1.73 m^2), eGFR decreased over time in both treatment groups. At 1year, mean eGFR was slightly lower, and at 4 years, mean eGFR was slightly higher in the dapagliflozin group compared with the placebo group.

4.9 Overdose

Dapagliflozin

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

Metformin 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 overdosage is suspected.

5. Pharmacological properties

5.1 Mechanism of Action

Dapagliflozin & Metformin Hydrochloride (ER) Tablets combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with Type 2 Diabetes: Dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and Metformin 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 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 response may actually decrease.

5.2 Pharmacodynamic properties

General

Dapagliflozin

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients with Type 2 Diabetes Mellitus following the administration of Dapagliflozin. Dapagliflozin doses of 5 or 10 mg per day in patients with Type 2 Diabetes Mellitus for 12 weeks resulted in excretion of approximately 70 grams of glucose in the urine per day. A near maximum glucose excretion was observed at the Dapagliflozin daily dose of 20 mg. This urinary glucose excretion with Dapagliflozin also results in increases in urinary volume.

Cardiac Electrophysiology

Dapagliflozin was not associated with clinically meaningful prolongation of QTc interval at daily doses up to 150 mg (15 times the recommended dose) in a study of healthy subjects. In addition, no clinically meaningful effect on QTc interval was observed following single doses of up to 500 mg (50 times the recommended dose) Dapagliflozin in healthy subjects.

5.3 Pharmacokinetics properties

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

Dapagliflozin

Absorption

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.

Distribution

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

Metabolism

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 [^{14}C]-Dapagliflozin dose and is the predominant drug-related component in human plasma.

Elimination

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [^{14}C]-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.

Specific Populations

Renal Impairment

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.

Hepatic Impairment

In patients with mild and moderate hepatic impairment (Child-Pugh Classes A and B), mean C_{max} 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 C_{max} and AUC of Dapagliflozin were up to 40% and 67% higher, respectively, as compared to healthy matched controls.

Geriatric

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.

Pediatric

Pharmacokinetics of Dapagliflozin & Metformin Hydrochloride (ER) Tablets in the pediatric population has not been studied.

Gender

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.

Race

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.

Body Weight

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

Metformin Hydrochloride

Absorption

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

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 Metformin850 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

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

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

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

Hepatic Impairment

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

Geriatric

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 C_{max} 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.

Gender

Metformin pharmacokinetic parameters did not differ significantly between healthy subjects and patients with Type 2 Diabetes when analyzed according to gender (males=19, females=16). Similarly, in controlled clinical studies in patients with Type 2 Diabetes, the antihyperglycemic effect of Metformin was comparable in males and females.

Race

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

6. Nonclinical properties

6.1 Animal toxicology or Pharmacology

No animal studies have been conducted with Dapagliflozin & Metformin Hydrochloride (ER) Tablets to evaluate carcinogenesis, mutagenesis, or impairment of fertility. The following data are based on the findings in the studies with Dapagliflozin and Metformin individually.

Dapagliflozin

Dapagliflozin did not induce tumors in either mice or rats at any of the doses evaluated in 2-year carcinogenicity studies. Oral doses in mice consisted of 5, 15, and 40 mg/kg/day in males and 2, 10, and 20 mg/kg/day in females, and oral doses in rats were 0.5, 2, and 10 mg/kg/day for both males and females. The highest doses evaluated in mice were approximately 72 times (males) and 105 times (females) the clinical dose of 10 mg/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

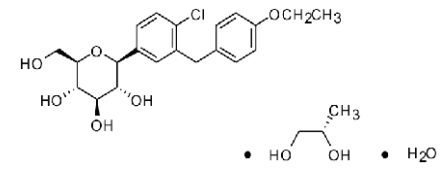
Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the MRHD of 2000 mg based on body surface area comparisons. 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.

7. Description

Dapagliflozin & Metformin Hydrochloride (ER) Tablets contain two oral antihyperglycemic medications used in the management of Type 2 Diabetes: Dapagliflozin and Metformin Hydrochloride.

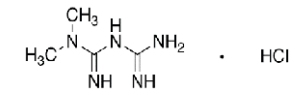
Dapagliflozin

Dapagliflozin is described chemically as D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]-phenyl]-, (1S)-, compounded with (2S)-1,2-propanediol, hydrate (1:1:1). The empirical formula is $C_{21}H_{25}ClO_6C3H_8O_2H_2O$ and the formula weight is 502.98. The structural formula is:



Metformin Hydrochloride

Metformin Hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5HCl$ and a molecular weight of 165.63. Metformin Hydrochloride is freely soluble in water, slightly soluble in alcohol, and is practically insoluble in acetone, ether, and chloroform. The pKa of Metformin is 12.4. The pH of a 1% aqueous solution of Metformin Hydrochloride is 6.68. The structural formula is:



8. Pharmaceutical particulars

8.1 Incompatibilities

NA

8.2 Shelf-life

Please refer details on blister / carton.

8.3 Packaging information

Alu-Alu blister of 10 tablets

8.4 Storage and handling instructions

Store at a temperature not exceeding 25°C. Protect from light and moisture.

9. Patient Counselling Information

What is the most important information I should know about Dapagliflozin & Metformin Hydrochloride (ER) Tablets?

Dapagliflozin & Metformin Hydrochloride (ER) Tablets can cause serious side effects, including:
- Lactic Acidosis. Metformin, one of the medicines in Dapagliflozin & Metformin Hydrochloride (ER) Tablets, can cause a rare but serious condition called lactic acidosis (a build-up of an acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in the hospital.

Call your doctor right away if you have any of the following symptoms, which could be signs of lactic acidosis:
- you feel cold in your hands or feet
- you feel dizzy or lightheaded
- you have a slow or irregular heartbeat
- you feel very weak or tired
- you have unusual (not normal) muscle pain
- you have trouble breathing
- you feel unusual sleepiness or sleep longer than usual
- you have stomach pains, nausea or vomiting

Most people who have had lactic acidosis with Metformin have other things that, combined with the Metformin use, led to the lactic acidosis. Tell your doctor if you have any of the following, because you have a higher chance for getting lactic acidosis with Dapagliflozin & Metformin Hydrochloride (ER) Tablets if you:
- have severe kidney problems or your kidneys are affected by certain x-ray tests that use injectable dye
- have liver problems
- drink alcohol very often, or drink a lot of alcohol in short-term "binge" drinking
- get dehydrated (lose a large amount of body fluids). This can happen if you are sick with a fever, vomiting, or diarrhea.
- Dehydration can also happen when you sweat a lot with activity or exercise and do not drink enough fluids
- have surgery
- have a heart attack, severe infection, or stroke.

The best way to keep from having a problem with lactic acidosis from Metforminis to tell your doctor if you have any of the problems in the list above. Your doctor may decide to stop your Dapagliflozin & Metformin Hydrochloride (ER) Tablets for a while if you have any of these things.

What is Dapagliflozin & Metformin Hydrochloride (ER) Tablets?

- Dapagliflozin & Metformin Hydrochloride (ER) Tablets contains 2 prescription medicines called Dapagliflozin and Metformin HCl. Dapagliflozin & Metformin Hydrochloride (ER) Tablets is used along with diet and exercise to improve blood sugar (glucose) control in adults with Type 2 Diabetes when treatment with either Dapagliflozin or Metformin has not controlled your blood sugar.
- Dapagliflozin & Metformin Hydrochloride (ER) Tablets is not for people with Type 1 Diabetes.
- Dapagliflozin & Metformin Hydrochloride (ER) Tablets is not for people with diabetic ketoacidosis (increased ketones in your blood or urine).
- It is not known if Dapagliflozin & Metformin Hydrochloride (ER) Tablets is safe and effective in children younger than 18 years of age.

Who should not take Dapagliflozin & Metformin Hydrochloride (ER) Tablets?

Do not take Dapagliflozin & Metformin Hydrochloride (ER) Tablets if you:
- have moderate to severe kidney problems or are on dialysis
- are allergic to Dapagliflozin, Metformin HCl, or any of the ingredients in Dapagliflozin & Metformin Hydrochloride (ER) Tablets. Symptoms of a serious allergic reaction to Dapagliflozin & Metformin Hydrochloride (ER) Tablets may include:
  - skin rash
  - raised red patches on your skin (hives)
  - swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing

If you have any of these symptoms, stop taking Dapagliflozin & Metformin Hydrochloride (ER) Tablets and contact your healthcare provider or go to the nearest hospital emergency room right away.
- have a condition called metabolic acidosis or diabetic ketoacidosis (increased ketones in your blood or urine).

What should I tell my healthcare provider before taking Dapagliflozin & Metformin Hydrochloride (ER) Tablets?

Before you take Dapagliflozin & Metformin Hydrochloride (ER) Tablets, tell your healthcare provider if you:
- have Type 1 Diabetes or have had diabetic ketoacidosis
- have moderate to severe kidney problems
- have liver problems
- have a history of urinary tract infections or problems urinating
- have heart problems, including congestive heart failure
- are going to have surgery
- are eating less due to illness, surgery or a change in your diet
- have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas
- drink alcohol very often, or drink a lot of alcohol in the short-term (“binge” drinking)
- have or have had bladder cancer
- are pregnant or plan to become pregnant. Dapagliflozin & Metformin Hydrochloride (ER) Tablets may harm your unborn baby. If you are pregnant or plan to become pregnant, talk to your healthcare provider about the best way to control your blood sugar.
- are breastfeeding or plan to breastfeed. It is not known if Dapagliflozin & Metformin Hydrochloride (ER) Tablets passes into your breast milk. Talk with your healthcare provider about the best way to feed your baby if you are taking Dapagliflozin & Metformin Hydrochloride (ER) Tablets.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Dapagliflozin & Metformin Hydrochloride (ER) Tablets may affect the way other medicines work and other medicines may affect the way Dapagliflozin & Metformin Hydrochloride (ER) Tablets works. Especially tell your healthcare provider if you take:
- water pills (diuretics)
- rifampin (used to treat or prevent tuberculosis)
- phenytoin or phenobarbital (used to control seizures)
- ritonavir (used to treat HIV infections)
- digoxin (used to treat heart problems)

Ask your healthcare provider for a list of these medicines if you are not sure if your medicine is listed above. Know the medicines you take. Keep a list of them and show it to you healthcare provider and pharmacist when you get a new medicine.

How should I take Dapagliflozin & Metformin Hydrochloride (ER) Tablets?

- Take Dapagliflozin & Metformin Hydrochloride (ER) Tablets exactly as your healthcare provider tells you to take it.
- Do not change your dose of Dapagliflozin & Metformin Hydrochloride (ER) Tablets without talking to your healthcare provider.
- Take Dapagliflozin & Metformin Hydrochloride (ER) Tablets by mouth 1 time each day with meals to lower your chance of an upset stomach. Talk to your healthcare provider about the best time of day for you.
- Swallow Dapagliflozin & Metformin Hydrochloride (ER) Tablets whole. Do not crush, cut, or chew Dapagliflozin & Metformin Hydrochloride (ER) Tablets.
- You may sometimes pass a soft mass in your stools (bowel movement) that looks like Dapagliflozin & Metformin Hydrochloride (ER) Tablets.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine you need may change. Tell your healthcare provider right away if you have any of these conditions and follow your healthcare provider's instructions.
- Stay on your prescribed diet and exercise program while taking Dapagliflozin & Metformin Hydrochloride (ER) Tablets.
- Your healthcare provider may do certain blood tests before you start Dapagliflozin & Metformin Hydrochloride (ER) Tablets and during your treatment.
- Your healthcare provider will check your diabetes with regular blood tests, including your blood sugar levels and your Hb1Ac.
- Follow your healthcare provider's instructions for treating low blood sugar (hypoglycemia). Talk to your healthcare provider if low blood sugar is a problem for you.
- If you miss a dose of Dapagliflozin & Metformin Hydrochloride (ER) Tablets, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take the medicine at the next regularly scheduled time.
- If you take too much Dapagliflozin & Metformin Hydrochloride (ER) Tablets, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while taking Dapagliflozin & Metformin Hydrochloride (ER) Tablets?

- Avoid drinking alcohol very often or drinking a lot of alcohol in a short period of time (“binge” drinking). It can increase your chances of getting serious side effects.

How should I store Dapagliflozin & Metformin Hydrochloride (ER) Tablets?

Store in a dry place at a temperature not exceeding 25°C. Protect from light.
Keep out of reach of children.

10. Details of manufacturer

Windlas Biotech Limited (Plant-3),
(WHO-GMP Certified Company)
Plot No. 39, Pharmacity, Selaqui,
Dehradun-248197, Uttarakhand.

11. Details of permission or licence number with date

Licence No.: 30/UA/2020, Date: 05/01/2024

12. Date of revision

NA

Marketed by:

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