To be sold by retail on the prescription of a R.M.P only

GLUCRETA M

WARNING: LACTIC ACIDOSIS

Lactic acidosis is a rare, but serious, complication that can occur due to metformin accumulation. The risk increases with conditions such as sepsis, dehydration, excess alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure. The onset of lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. Laboratory abnormalities include low pH, increased anion gap, and elevated blood lactate. If acidosis is suspected, Dapagliflozin and metformin hydrochloride extended-release tablets should be discontinued and the patient hospitalized immediately.

1. **Generic Name**

   Dapagliflozin and Metformin Hydrochloride Extended-Release Tablets

2. **Qualitative and quantitative composition**

GLUCRETA M 10+1000

Each film coated tablet contains:

Dapagliflozin……10 mg

Metformin hydrochloride I.P. (In Extended release form) …. 1000 mg

Excipients…….q.s.

Color: Yellow oxide of iron and Titanium dioxide I.P.

The excipients used are Lactose Anhydrous, Microcrystalline Cellulose, Croscarmellose Sodium, Povidone, Isopropyl alcohol, Colloidal silicon dioxide, Yellow oxide of iron, Magnesium stearate, Sodium carboxymethyl cellulose, Hypromellose, Talc, Polyvinyl alcohol, Titanium Dioxide, Macrogol/PEG.

GLUCRETA M 5+1000

Each film coated tablet contains:

Dapagliflozin……5 mg

Metformin hydrochloride I.P. (In Extended release form) …. 1000 mg

Excipients…….q.s.

Color: Yellow oxide of Iron, Red oxide of iron and Titanium dioxide I.P.

The excipients used are Lactose anhydrous, Microcrystalline cellulose, Croscarmellose sodium, Povidone, Isopropyl alcohol, Colloidal silicon dioxide, Yellow oxide of iron, Magnesium stearate,Sodium carboxymethyl cellulose, Hypromellose, Talc, Polyvinyl alcohol, Titanium Dioxide, Macrogol/PEG, Red oxide of iron..

GLUCRETA M 10+500

Each film coated tablet contains:

Dapagliflozin…….10 mg

Metformin hydrochloride I.P. (In Extended release form) …. 500 mg

Excipients…….q.s.

Color: Yellow oxide of iron, Red oxide of iron and Titanium dioxide I.P.

The excipients used are Lactose anhydrous, Microcrystalline cellulose, Croscarmellose sodium, Povidone, Isopropyl alcohol, Colloidal silicon dioxide, Yellow oxide of iron, Magnesium stearate, Sodium carboxymethyl cellulose, Hypromellose, Talc, Polyvinyl alcohol, Titanium Dioxide, Macrogol/PEG, Red oxide of iron.

GLUCRETA M 5+500

Each film coated tablet contains:

Dapagliflozin……..5 mg

Metformin hydrochloride I.P. (In Extended release form)…. 500 mg

Excipients…….q.s.

Color: Yellow oxide of iron, Sunset Yellow FCF and Titanium dioxide I.P.

The excipients used are Lactose anhydrous, Microcrystalline cellulose, Croscarmellose sodium, Povidone, Isopropyl alcohol, Colloidal silicon dioxide, Yellow oxide of iron, Magnesium stearate, Sodium carboxymethyl cellulose, Hypromellose, Talc, Polyvinyl alcohol, Titanium Dioxide, Macrogol/PEG, Sunset Yellow FCF.

3. Dosage form and strength

Dosage Form: Tablets Strengths:

- **GLUCRETA M 5+500 : 5** mg dapagliflozin/500 mg metformin HCl extended-release
- **GLUCRETA M 5+1000 : 5** mg dapagliflozin/1000 mg metformin HCl extendedrelease
- **GLUCRETA M 10+500 :** 10 mg dapagliflozin/500 mg metformin HCl extendedrelease
- **GLUCRETA M 10+1000 :** 10 mg dapagliflozin/1000 mg metformin HCl extendedrelease

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

Healthcare providers should individualize the starting dose of Medicine based on the patient's current treatment.

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

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

Dosing may be adjusted based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 10 mg dapagliflozin and 2000 mg metformin HCl.

In patients with volume depletion, correcting this condition prior to initiation of Medicine is recommended.

Patients with Renal Impairment

No dosage adjustment for dapagliflozin and metformin hydrochloride extended-release tablets is indicated in patients with mild renal impairment (eGFR of 60 mL/min/1.73 m2 or greater).

Assessment of renal function is recommended prior to initiation of dapagliflozin and metformin hydrochloride extended-release tablets therapy and periodically thereafter.

Tablets should be swallowed whole & not chewed or crushed.

4.3 Contraindications

GLUCRETA M is contraindicated in patients with:

- Moderate to severe renal impairment (e.g., serum creatinine levels ≥1.5 mg/dL for men, ≥1.4 mg/dL for women, or eGFR <60 mL/min/1.73 m2 or CrCl <60 mL/min), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia.
- History of a serious hypersensitivity reaction to dapagliflozin or hypersensitivity to metformin hydrochloride.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

4.4 Special warnings and precautions for use

Lactic Acidosis

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with dapagliflozin and metformin hydrochloride extended-release tablets; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypo perfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypo perfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypo perfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake when taking metformin since alcohol

potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure
The onset of lactic acidosis often is subtle and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant Brady arrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur. Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease. Levels of fasting venous plasma lactate above the upper limit of normal (ULN), but <5 mmol/L, in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt haemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery [see *Contraindications* and *Warnings and Precautions]*

Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in patients with type 1 and type 2 diabetes mellitus receiving sodium-glucose cotransporter 2 (SGLT2) inhibitors, including dapagliflozin. Fatal cases of ketoacidosis have been reported in patients taking dapagliflozin. Dapagliflozin and metformin hydrochloride extended-release tablets are not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with dapagliflozin and metformin hydrochloride extended-release tablets who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels as ketoacidosis associated with dapagliflozin may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, dapagliflozin and metformin hydrochloride extended-release tablets should be discontinued, the patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid, and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized, and the institution of treatment was delayed because the presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and

symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis, such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating dapagliflozin and metformin hydrochloride extended-release tablets, consider factors in the patient history that may predispose to ketoacidosis, including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

For patients who undergo scheduled surgery, consider temporarily discontinuing dapagliflozin and metformin hydrochloride extended-release tablets for at least 3 days prior to surgery.

Consider monitoring for ketoacidosis and temporarily discontinuing dapagliflozin and metformin hydrochloride extended-release tablets in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting dapagliflozin and metformin hydrochloride extended-release tablets.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue dapagliflozin and metformin hydrochloride extended-release tablets and seek medical attention immediately if signs and symptoms occur.

Acute Kidney Injury

Dapagliflozin causes intravascular volume contraction (*see Warning and Precautions)*, and can cause acute kidney injury. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving dapagliflozin and metformin hydrochloride extended-release tablets.

Increases in serum creatinine and decreases in estimated GFR may also be observed with initiation of dapagliflozin and metformin hydrochloride extended-release tablets. Elderly patients and patients with impaired renal function may be more susceptible to these changes. Before initiating dapagliflozin and metformin hydrochloride extendedrelease 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 and metformin hydrochloride extended-release tablets in the setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue dapagliflozin and metformin hydrochloride extended-release tablets promptly and institute treatment.

Renal function should be evaluated prior to initiation of dapagliflozin and metformin hydrochloride extended-release tablets and monitored periodically thereafter. Use of dapagliflozin and metformin hydrochloride extended-release tablets is not recommended when the eGFR is less than 45 mL/min/1.73 m^2 and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2.

Urosepsis and Pyelonephritis

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

Hypoxic States

Cardiovascular collapse (shock), acute congestive heart failure, acute myocardial infarction, and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on dapagliflozin and metformin hydrochloride extended-release tablets therapy, the drug should be promptly discontinued.

Use in Patients with Renal Impairment

Metformin is known to be substantially excreted by the kidney and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Therefore, dapagliflozin and metformin hydrochloride extended-release tablets is contraindicated in patients with moderate to severe renal impairment. Also, 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

Before initiation of dapagliflozin and metformin hydrochloride extended-release tablets therapy, and at least annually thereafter, renal function should be assessed and verified as normal or mildly impaired. In patients in whom development of renal impairment is anticipated (e.g., elderly), renal function should be assessed more frequently and dapagliflozin and metformin hydrochloride extended-release tablets discontinued if evidence of moderate to severe renal impairment is present.

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 this medicine 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.

Impaired Hepatic Function

Metformin use in patients with impaired hepatic function has been associated with some cases of lactic acidosis. Therefore, dapagliflozin and metformin hydrochloride extendedrelease tablets should generally be avoided in patients with hepatic impairment.

Alcohol Intake

Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving dapagliflozin and metformin hydrochloride extended-release tablets

Surgical Procedures

Use of dapagliflozin and metformin hydrochloride extended-release tablets should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the

patient's oral intake has resumed and renal function has been evaluated as normal or mildly impaired.

Change in Clinical Status of Patients with Previously Controlled Type 2 Diabetes

A patient with type 2 diabetes, previously well controlled on dapagliflozin and metformin hydrochloride extended-release tablets, who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, dapagliflozin and metformin hydrochloride extended-release tablets must be stopped immediately and other appropriate corrective measures initiated.

Use with Medications Known to Cause Hypoglycemia

Dapagliflozin

Insulin and insulin secretagogues are known to cause hypoglycemia. Dapagliflozin can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue

Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when these agents are used in combination with dapagliflozin and metformin hydrochloride extended-release 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.

Concomitant Medications Affecting Renal Function or Metformin Disposition

Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion, should be used with caution.

Radiologic Studies with Intravascular Iodinated Contrast Materials

Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, dapagliflozin and metformin hydrochloride extended-release tablets should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal or mildly impaired.

Vitamin B_{12} Concentrations

In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. This decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex is, however,

very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on dapagliflozin and metformin hydrochloride extended-release 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.

Necrotizing Fasciitis of the Perineum (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 (SGLT2) inhibitors. This serious rare infection, called necrotizing fasciitis of the perineum, is also referred to as Fournier's gangrene.

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

Increases in LDL-C occur with dapagliflozin. Monitor LDL-C and treat per standard of care after initiating dapagliflozin and metformin hydrochloride extended-release 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 preexisting bladder tumors. Consequently, dapagliflozin and metformin hydrochloride extended-release 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 and metformin hydrochloride extended-release tablets should be considered.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with dapagliflozin and metformin hydrochloride extended-release tablets or any other antidiabetic drug.

4.5 Drugs 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 1,5AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

Cationic Drugs

Metformin hydrochloride

Cationic drugs (e.g., amiloride, cimetidine, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. A 40% increase in exposure (AUC) of metformin when coadministered with cimetidine was observed in normal healthy volunteers. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of dapagliflozin and metformin hydrochloride extended-release tablets and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Use with Other Drugs

Metformin hydrochloride

Some medications can predispose to hyperglycemia and may lead to loss of glycemic control. These medications include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving dapagliflozin and metformin hydrochloride extended-release tablets, the patient should be observed closely for loss of glycemic control. When such drugs are withdrawn from a patient receiving Dapagliflozin and Metformin Hydrochloride Extended-Release 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 co-administered in single-dose interaction studies.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy Category C

There are no adequate and well-controlled studies of dapagliflozin and metformin hydrochloride extended-release tablets or its individual components in pregnant women reported. Based on results of reported reproductive and developmental toxicity studies

in animals, dapagliflozin, a component of dapagliflozin and metformin hydrochloride extended-release tablets, may affect renal development and maturation. In a reported 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 and metformin hydrochloride extended-release tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Dapagliflozin

In a reported 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 reported 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 reported 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 nor 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 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.

Nursing Mothers

It is not known whether dapagliflozin and metformin hydrochloride extended-release tablets is excreted in human milk. In reported studies which were 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.

In Reported study data, when 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 locational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from dapagliflozin, a decision should be made whether to discontinue nursing or to discontinue dapagliflozin and metformin hydrochloride extended-release tablets, taking into account the importance of the drug to the mother

Pediatric Use

This medicine is not recommended for children and adolescents under 18 years of age, because it has not been studied in these patients.

Geriatric Use

Dapagliflozin and metformin hydrochloride extended-release tablets

No Dapagliflozin and Metformin Hydrochloride Extended-Release Tablets dosage change is recommended based on age. More frequent assessment of renal function is recommended in elderly patients.

Dapagliflozin

In reported clinical study, 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

The reported 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, dapagliflozin and metformin hydrochloride extended-release tablets should only be used in patients with normal or mildly impaired renal function. The initial and maintenance dosing of metformin should be conservative in patients with advanced age due to the potential for decreased renal function in this population. Any dose adjustment should be based on a careful assessment of renal function.

Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. GLUCRETA M is not recommended in patients with hepatic impairment

Dapagliflozin

In this reported clinical safety and efficacy studies, the pool of 21 double-blind, active- and placebo-controlled (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.

4.7 Effects on ability to drive and use machines

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

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

•Use in Patients with Renal Impairment

•Hypotension

•Use with Medications Known to Cause Hypoglycemia

•Vitamin B12 Concentrations

•Genital Mycotic Infections

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

•Bladder Cancer

Clinical Trials Experience

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

Dapagliflozin and Metformin hydrochloride

Data from this reported clinical safety and efficacy studies a prespecified pool of patients from 8 short-term, placebo-controlled studies of dapagliflozin coadministered with metformin immediate-or extended-release was used to evaluate safety. This pool included several add-on studies (metformin alone and in combination with a dipeptidyl peptidase-4 [DPP4] inhibitor and metformin, or insulin and metformin, 2 initial combinations with metformin studies, and 2 studies of patients with cardiovascular disease [CVD] and type 2 diabetes who received their usual treatment [with metformin as background therapy]). For studies that included background therapy with and without metformin, only patients who received metformin were included in the 8-study placebocontrolled pool. Across these 8 studies 983 patients were treated once daily with dapagliflozin 10 mg and metformin and 1185 were treated with placebo and metformin. These 8 studies provide a mean duration of exposure of 23 weeks. The mean age of the population was 57 years and 2% were older than 75 years. Fifty-four percent (54%) of the population was male; 88% White, 6% Asian, and 3% Black or African American. At baseline, the population had diabetes for an average of 8 years, mean hemoglobin A1c (HbA1c) was 8.4%, and renal function was normal or mildly impaired in 90% of patients and moderately impaired in 10% of patients. The overall incidence of adverse events for the 8-study, short-term, placebo-controlled pool in patients treated with dapagliflozin 10 mg and metformin was 60.3% compared to 58.2% for the placebo and metformin group. Discontinuation of therapy due to adverse events in patients who received dapagliflozin

10 mg and metformin was 4% compared to 3.3% for the placebo and metformin group. The most commonly reported events leading to discontinuation and reported in at least 3 patients treated with dapagliflozin 10 mg and metformin were renal impairment (0.7%), increased blood creatinine (0.2%), decreased renal creatinine clearance (0.2%), and urinary tract infection (0.2%).

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

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

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

Dyslipidemia	1.4	2.7	1.5

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

Adverse Reaction	% of Patients		
	Pool of 8 Placebo-Controlled Studies		
	Placebo and Metformin N=1185	Dapagliflozin 5 mg and Metformin N=410	Dapagliflozin 10 mg and Metformin N=983
Pharyngitis	1.1	2.7	1.5
Increased urination§	1.4	2.4	2.6
Discomfort with urination	1.1	2.2	1.6

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

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

‡ Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for males: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection, posthitis, and balanoposthitis. (N for males: Placebo and metformin=651, dapagliflozin 5 mg and metformin=187, dapagliflozin 10 mg and metformin=553).

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

Metformin hydrochloride

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

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

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

These data reflect exposure of 2338 patients to dapagliflozin with a mean exposure duration of 21 weeks. Patients received placebo (N=1393), dapagliflozin 5 mg (N=1145), or dapagliflozin 10 mg (N=1193) once daily. The mean age of the population was 55 years and 2% were older than 75 years of age. Fifty percent (50%) of the population were male; 81% were White, 14% were Asian, and 3% were Black or African American. At baseline, the population had diabetes for an average of 6 years, had a mean HbA1c of 8.3%, and 21% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired in 92% of patients and moderately impaired in 8% of patients (mean eGFR 86 mL/min/1.73 m^2).

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

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

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

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

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

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

§ Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for males: balanitis, fungal genital infection, balanitis candida, genital candidiasis, and genital infection male, penile dapagliflozin 5 mg=564, dapagliflozin 10 mg=595).

Pool of 13 Placebo-Controlled Studies for Dapagliflozin 10 mg

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

Volume Depletion

Dapagliflozin causes an osmotic diuresis, which may lead to reductions in intravascular volume. Adverse reactions related to volume depletion (including reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension) are shown in Table 3 for the 12study and 13-study, short-term, placebo-controlled pools.

Adverse Reactions of Volume Depletion* in Clinical Studies with Dapagliflozin

	Pool of 12 Placebo-Controlled Studies			**Pool of 13 Placebo-Controlled Studies**	
	Placebo	**Dapagliflozin 5 mg**	**Dapagliflozin 10 mg**	**Placebo**	**Dapagliflozin 10 mg**
Overall population N (%)	N=1393 5 (0.4%)	N=1145 7 (0.6%)	N=1193 9 (0.8%)	N=2295 17 (0.7%)	N=2360 27 (1.1%)
Patient Subgroup n (%)					

Patients on loop diuretics	n=55 1 (1.8%)	n=40 0	n=31 3 (9.7%)	n=267 4 (1.5%)	n=236 6 (2.5%)
Patients with moderate renal impairment with eGFR ≥30 and <60 mL/min/1.73 m2	n=107 2 (1.9%)	n=107 1 (0.9%)	n=89 1 (1.1%)	n=268 4 (1.5%)	n=265 5 (1.9%)
Patients ≥65 years of age	n=276 1 (0.4%)	n=216 1 (0.5%)	n=204 3 (1.5%)	n=711 6 (0.8%)	n=665 11 (1.7%)

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

Impairment of Renal Function

Use of dapagliflozin was associated with increases in serum creatinine and decreases in eGFR (see Table 4). In patients with normal or mildly impaired renal function at baseline, serum creatinine and eGFR returned to baseline values at Week 24. Renal-related adverse reactions, including renal failure and blood creatinine increase, were more frequent in patients treated with dapagliflozin (see Table below). Elderly patients and patients with impaired renal function were more susceptible to these adverse reactions (see Table below). Sustained decreases in eGFR were seen in patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2).

Changes in Serum Creatinine and eGFR Associated with Dapagliflozin in the Pool of 12 Placebo-Controlled Studies and Moderate Renal Impairment Study

		Pool of 12 Placebo-Controlled Studies		
		Placebo N=1393	**Dapagliflozin 5 mg N=1145**	**Dapagliflozin 10mg N=1193**
Baseline Mean	Serum Creatinine (mg/dL)	0.853	0.860	0.847
	eGFR (mL/min/1.73 m^2)	86.0	85.3	86.7
Week 1 Change	Serum Creatinine (mg/dL)	−0.003	0.029	0.041
	eGFR (mL/min/1.73 m^2)	0.4	−2.9	−4.1

Week 24 Change	Serum Creatinine (mg/dL)	−0.005	−0.001	0.001
	eGFR (mL/min/1.73 m^2)	0.8	0.8	0.3
		Moderate Renal Impairment Study		
		Placebo N=84	**Dapagliflozin 5 mg N=83**	**Dapagliflozin 10 mg N=85**
Baseline Mean	Serum Creatinine (mg/dL)	1.46	1.53	1.52
	eGFR (mL/min/1.73 m^2)	45.6	44.2	43.9
Week 1 Change	Serum Creatinine (mg/dL)	0.01	0.13	0.18
	eGFR (mL/min/1.73 m^2)	0.5	−3.8	−5.5
Week 24 Change	Serum Creatinine (mg/dL)	0.02	0.08	0.16
	eGFR (mL/min/1.73 m^2)	0.03	−4.0	−7.4
Week 52 Change	Serum Creatinine (mg/dL)	0.10	0.06	0.15
	eGFR (mL/min/1.73 m^2)	−2.6	−4.2	−7.3

Proportion of Patients with at Least One Renal Impairment- Related Adverse Reaction

Pool of 6 reported Placebo-Controlled Studies (up to 104 weeks)*				**Pool of 9 reported Placebo- Controlled Studies (up to 104 weeks)†**	
Baseline Characteristic	**Placebo**	**Dapagliflozin 5 mg**	**Dapagliflozin 10 mg**	**Placebo**	**Dapagliflozin 10 mg**
Overall population Patients (%) with at least one event	n=785 13(1.%)	n=767 14 (1.8%)	n=859 16 (1.9%)	n=1956 82 (4.2%)	n=2026 136 (6.7%)

65 years of age and older Patients (%) with at least one event	n=190 4(2.1%)	n=162 5 (3.1%)	n=159 6 (3.8%)	n=655 52 (7.9%)	n=620 87 (14.0%)
eGFR ≥30 and <60 mL/min/1.73 m2 Patients (%) with at least one event	n=77 5(6.5%)	n=88 7 (8.0%)	n=75 9 (12.0%)	n=249 40 (16.1%)	n=251 71 (28.3%)
65 years of age and older and eGFR ≥30 and <60 mL/min/1.73 m2 Patients (%) with at least one event	n=41 2(4.9%)	n=43 3 (7.0%)	n=35 4 (11.4%)	n=141 27 (19.1%)	n=134 47 (35.1%)

*** Subset of patients from the pool of 12 placebo-controlled studies with long-**term extensions.

† Subset of patients from the pool of 13 placebo-controlled studies with long-term extensions.

The safety of dapagliflozin was evaluated in a study of patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m2). In this study 13 patients experienced bone fractures for treatment durations up to 104 weeks. No fractures occurred in the placebo group, 5 occurred in the dapagliflozin 5 mg group, and 8 occurred in the dapagliflozin 10 mg group. Eight of these 13 fractures were in patients who had a baseline eGFR of 30 to 45 mL/min/1.73 m2. Eleven of the 13 fractures were reported within the first 52 weeks. There was no apparent pattern with respect to the anatomic site of fracture.

Hypoglycemia

The frequency of hypoglycemia by study is shown in Table below. Hypoglycemia was more frequent when dapagliflozin was added to sulfonylurea or insulin.

Incidence of Major* and Minor† Hypoglycemia in Placebo-Controlled Studies

	Placebo	**Dapagliflozin 5 mg**	**Dapagliflozin 10 mg**
Add-on to Metformin* (24 weeks)	**N=137**	**N=137**	**N=135**

Major [n (%)]	0	0	0
Minor [n (%)]	0	2 (1.5)	1 (0.7)
Active Control Add-on to Metformin versus Glipizide (52 weeks)	**N=408**	–	**N=406**
Major [n (%)]	3 (0.7)	–	0
Minor [n (%)]	147 (36.0)	–	7 (1.7)
Add-on to DPP4 inhibitor (with or without Metformin) (24 weeks)	**N=226**	–	**N=225**
Major [n (%)]	0	–	1 (0.4)
Minor [n (%)]	3 (1.3)	–	4 (1.8)
Add-on to Insulin with or without other OADs‡ (24 weeks)	**N=197**	**N=212**	**N=196**
Major [n (%)]	1 (0.5)	1 (0.5)	1 (0.5)
Minor [n (%)]	67 (34.0)	92 (43.4)	79 (40.3)

* Major episodes of hypoglycemia were defined as symptomatic episodes requiring external (third party) assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value <54 mg/dL and prompt recovery after glucose or glucagon administration.

† Minor episodes of hypoglycemia were defined as either a symptomatic episode with a capillary or plasma glucose measurement <63 mg/dL regardless of need for external assistance, or an asymptomatic capillary or plasma glucose measurement <63 mg/dL that does not qualify as a major episode.

‡ OAD = oral antidiabetic therapy**.**

Genital Mycotic Infections

Genital mycotic infections were more frequent with dapagliflozin treatment. In reported study genital mycotic infections were reported in 0.9% of patients on placebo, 5.7% on dapagliflozin 5 mg, and 4.8% on dapagliflozin 10 mg, in the 12-study placebo-controlled pool. Discontinuation from study due to genital infection occurred in 0% of placebotreated patients and 0.2% of patients treated with dapagliflozin 10 mg. Infections

were more frequently reported in females than in males (see Table 2). The most frequently reported genital mycotic infections were vulvovaginal mycotic infections in females and balanitis in males. Patients with a history of genital mycotic infections were more likely to have a genital mycotic infection during the study than those with no prior history (10.0%, 23.1%, and 25.0% versus 0.8%, 5.9%, and 5.0% on placebo, dapagliflozin 5 mg, and dapagliflozin 10 mg, respectively).

Hypersensitivity Reactions

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

Laboratory Tests

Increase in Hematocrit

Dapagliflozin

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

Increase in Serum Inorganic Phosphorus

Dapagliflozin

In the pool of 13 placebo-controlled reported studies, increases from baseline in mean serum phosphorus levels were reported at Week 24 in dapagliflozin 10 mg–treated patients compared with placebo-treated patients (mean increases of 0.13 mg/dL versus −0.04 mg/dL, respectively). Higher proportions of patients with marked laboratory abnormalities of hyperphosphatemia (≥5.6 mg/dL if age 17-65 or ≥5.1 mg/dL if age ≥66) were reported in the dapagliflozin 10 mg group versus the placebo group at Week 24 (1.7% versus 0.9%, respectively).

Increase in Low-Density Lipoprotein Cholesterol Dapagliflozin

Dapagliflozin

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

Vitamin B12 Concentrations

Metformin hydrochloride

Metformin may lower serum vitamin B12 concentrations. Measurement of hematologic parameters on an annual basis is advised in patients on dapagliflozin and metformin

hydrochloride extended-release tablets and any apparent abnormalities should be appropriately investigated and managed.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

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 [see Warnings and Precautions (5.1)]. 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 and Metformin Hydrochloride Extended-Release Tablets combine 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 biguanides.

Dapagliflozin

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

Metformin hydrochloride

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

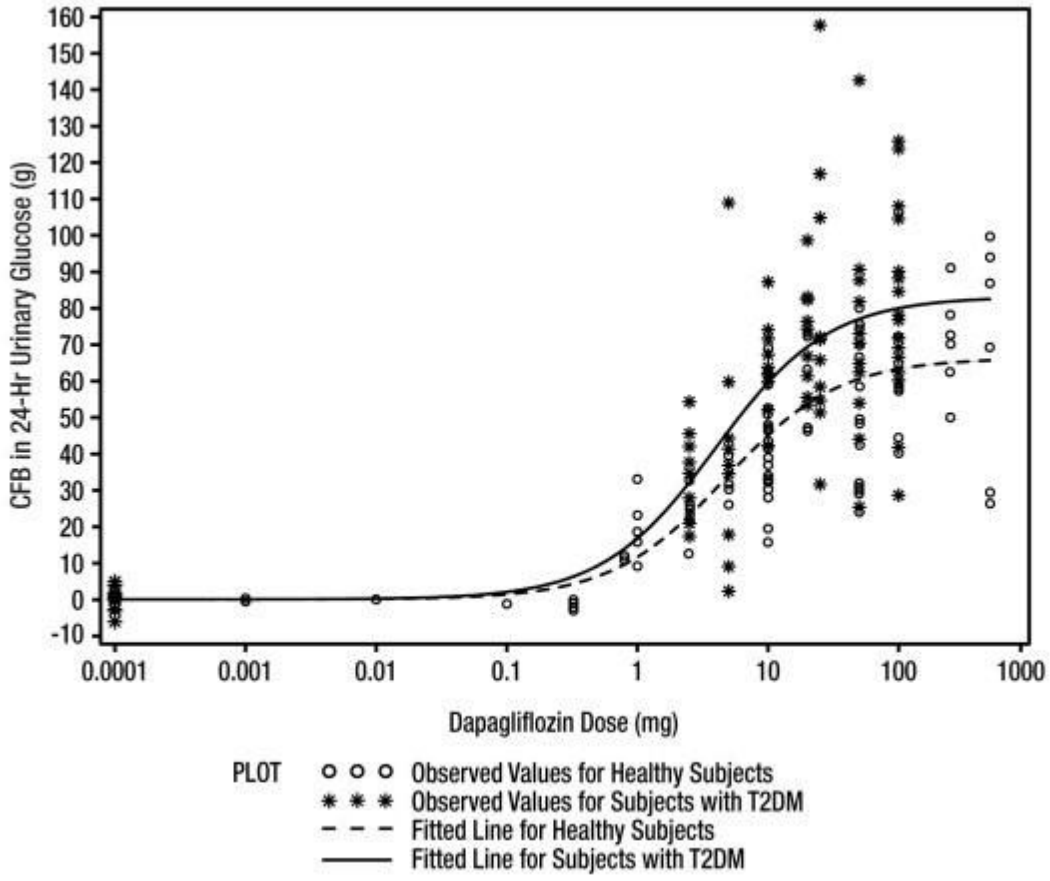
5.2 Pharmacodynamic properties

General

Dapagliflozin

In reported study Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following the administration of dapagliflozin (see Figure 1). 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

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



Cardiac Electrophysiology

Dapagliflozin was not associated with clinically meaningful prolongation of QTc interval at daily doses up to 150 mg (15 times the recommended 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 Pharmacokinetic properties

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

Absorption

Dapagliflozin

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

Metformin hydrochloride

Following a single oral dose of metformin extended-release, Cmax is achieved with a median value of 7 hours and a range of 4 to 8 hours. The extent of metformin absorption (as measured by AUC) from the metformin extended-release tablet increased by approximately 50% when given with food. There was no effect of food on Cmax and Tmax of metformin.

Distribution

Dapagliflozin

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

Metformin hydrochloride

Distribution studies with extended-release metformin have not been conducted; however, the apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes.

Metabolism

Dapagliflozin

The metabolism of dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearance pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61% of a 50 mg [14C]dapagliflozin dose and is the predominant drug-related component in human plasma.

Metformin hydrochloride

Intravenous single-dose studies in healthy subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion.

Metabolism studies with extended-release metformin tablets have not been conducted.

Elimination

Dapagliflozin

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [14C]-dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively. In urine, less than 2% of the dose is excreted as parent drug. In feces, Approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life (t½) for dapagliflozin is approximately 12.9 hours following a single oral dose of dapagliflozin 10 mg.

Metformin hydrochloride

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

Specific Populations

Renal Impairment

Dapagliflozin and Metformin Hydrochloride Extended-Release Tablets

Use of metformin in patients with renal impairment increases the risk for lactic acidosis. Because it contains metformin, Dapagliflozin and Metformin Hydrochloride ExtendedRelease Tablets is contraindicated in patients with moderate to severe renal impairment.
No dose adjustment of drug is required in patients with mild renal impairment

Dapagliflozin

In a reported study 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%, 2.04fold, and 3.03-fold higher, respectively, as compared to patients with type 2 diabetes with normal renal function. Higher systemic exposure of dapagliflozin in patients with type 2 diabetes mellitus with renal impairment did not result in a correspondingly higher

24-hour glucose excretion. The steady-state 24-hour urinary glucose excretion in patients with type 2 diabetes and mild, moderate, and severe renal impairment was 42%, 80%, and 90% lower, respectively, than in patients with type 2 diabetes with normal renal function. The impact of hemodialysis on dapagliflozin exposure is not known.

Metformin hydrochloride

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Hepatic Impairment

Dapagliflozin and metformin hydrochloride extended-release tablets

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Because drug contains metformin, it should generally be avoided in patients with hepatic impairment

Dapagliflozin

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

Metformin hydrochloride

No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment. ***Geriatric***

Dapagliflozin

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

Metformin hydrochloride

Limited data from reported controlled pharmacokinetic studies of metformin in healthy elderly subjects suggests that total plasma clearance of metformin is decreased, the halflife is prolonged, and Cmax is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Dapagliflozin and metformin hydrochloride extended-release tablets should not be initiated in patients of any age unless measurement of creatinine clearance demonstrates that renal function is only normal or mildly impaired.

Pediatric

Pharmacokinetics of Dapagliflozin and metformin hydrochloride extended-release tablets in the pediatric population has not been studied.

Gender

Dapagliflozin

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

Metformin hydrochloride

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

Race

Dapagliflozin

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

Metformin hydrochloride

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

Body Weight

Dapagliflozin

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

Drug Interactions

Specific pharmacokinetic drug interaction studies with dapagliflozin and metformin hydrochloride extended-release tablets have not been performed, although such studies have been conducted with the individual dapagliflozin and metformin components.

In Vitro Assessment of Drug Interactions

Dapagliflozin

In reported *in vitro* studies, dapagliflozin and dapagliflozin 3-O-glucuronide neither inhibited CYP 1A2, 2C9, 2C19, 2D6, 3A4, nor induced CYP 1A2, 2B6, or 3A4. Dapagliflozin is a weak substrate of the P-glycoprotein (P-gp) active transporter, and dapagliflozin 3-O-glucuronide is a substrate for the OAT3 active transporter. Dapagliflozin or dapagliflozin 3-O-glucuronide did not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 active transporters. Overall, dapagliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are P-gp, OCT2, OAT1, or OAT3 substrates.

Effects of Other Drugs on Metformin

Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

Coadministered Drug (Dose Regimen)*	**Metformin (Dose Regimen)***	**Metformin**	
		Change† in AUC‡	**Change† in Cmax**
No dosing adjustments required for the following:			
Glyburide (5 mg)	850 mg	↓9%§	↓7%§
Furosemide (40 mg)	850 mg	↑15%§	↑22%§
Nifedipine (10 mg)	850 mg	↑9%	↑20%
Propranolol (40 mg)	850 mg	↓10%	↓6%
Ibuprofen (400 mg)	850 mg	↑5%§	↑7%§
Cationic drugs eliminated by renal tubular secretion may reduce metformin elimination: use with caution.			
Cimetidine (400 mg)	850 mg	↑40%	↑60%

* All metformin and coadministered drugs were given as single doses.

† Percent change (with/without coadministered drug and no change = 0%); ↑ and ↓ indicate the exposure increase and decrease, respectively.

‡ AUC = AUC (INF).

§ Ratio of arithmetic means.

Below shows the effect of metformin on other coadministered drugs.

Effect of Metformin on Coadministered Drug Systemic Exposure

Coadministered Drug (Dose	**Metformin (Dose**	**Coadministered Drug**

Regimen)*	Regimen)*	Change† in AUC‡	Change † in Cmax
No dosing adjustments required for the following:			
Glyburide (5 mg)	850 mg	↓22%§	↓37%§
Furosemide (40 mg)	850 mg	↓12%§	↓31%§
Nifedipine (10 mg)	850 mg	↑10%	↑8%
Propranolol (40 mg)	850 mg	↑1%¶	↑2%
Ibuprofen (400 mg)	850 mg	↓3%#	↑1%#
Cimetidine (400 mg)	850 mg	↓5%¶	↑1%

* All metformin and coadministered drugs were given as single doses.

† Percent change (with/without coadministered drug and no change = 0%); ↑ and ↓ indicate the exposure increase and decrease, respectively.

‡ AUC = AUC (INF) unless otherwise noted. §

Ratio of arithmetic means, p-value of difference <0.05. ¶

AUC (0-24 hr) reported. # Ratio

of arithmetic means.

Effects of Other Drugs on Dapagliflozin

Table below shows the effect of coadministered drugs on dapagliflozin. No dose adjustments are recommended for dapagliflozin.

Effects of Coadministered Drugs on Dapagliflozin Systemic Exposure

Coadministered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Dapagliflozin	
		Change† in AUC‡	Change† in Cmax

No dosing adjustments required for the following:			
Oral Antidiabetic Agents			
Metformin (1000 mg)	20 mg	↓1%	↓7%
Pioglitazone (45 mg)	50 mg	0%	↑9%
Sitagliptin (100 mg)	20 mg	↑8%	↓4%
Glimepiride (4 mg)	20 mg	↓1%	↑1%
Voglibose (0.2 mg three times daily)	10 mg	↑1%	↑4%
Cardiovascular Agents			
Hydrochlorothiazide (25 mg)	50 mg	↑7%	↓1%
Bumetanide (1 mg)	10 mg once daily for 7 days	↑5%	↑8%
Valsartan (320 mg)	20 mg	↑2%	↓12%
Simvastatin (40 mg)	20 mg	↓1%	↓2%
Anti-infective Agent			
Rifampin (600 mg once daily for 6 days)	10 mg	↓22%	↓7%
Non-Steroidal Anti-inflammatory Agent			

Mefenamic Acid (loading dose of 500 mg followed by 14 doses of 250 mg every 6 hours)	10 mg	↑51%	↑13%

* Single dose unless otherwise noted.

† Percent change (with/without coadministered drug and no change = 0%); ↑ and ↓ indicate the exposure increase and decrease, respectively.

‡ AUC = AUC (INF) for drugs given as single dose and AUC = AUC (TAU) for drugs given in multiple doses.

Effects of Dapagliflozin on Other Drugs

Table 10 shows the effect of dapagliflozin on other coadministered drugs. Dapagliflozin did not meaningfully affect the pharmacokinetics of the coadministered drugs.

Effects of Dapagliflozin on the Systemic Exposures of Coadministered Drugs

Coadministered Drug (Dose Regimen)*	**Dapagliflozi n (Dose Regimen)***	**Coadministered Drug**	
		Change† in AUC‡	**Change † in Cmax**
No dosing adjustments required for the following:			
Oral Antidiabetic Agents			
Metformin (1000 mg)	20 mg	0%	↓5%
Pioglitazone (45 mg)	50 mg	0%	↓7%
Sitagliptin (100 mg)	20 mg	↑1%	↓11%
Glimepiride (4 mg)	20 mg	↑13%	↑4%
Cardiovascular Agents			
Hydrochlorothiazide (25 mg)	50 mg	↓1%	↓5%

Bumetanide (1 mg)	10 mg once daily for 7 days	↑13%	↑13%
Valsartan (320 mg)	20 mg	↑5%	↓6%
Simvastatin (40 mg)	20 mg	↑19%	↓6%
Digoxin (0.25 mg)	20 mg loading dose then 10 mg once daily for 7 days	0%	↓1%
Warfarin (25 mg) S-warfarin Rwarfarin	20 mg loading dose then 10 mg once daily for 7 days	↑3% ↑6%	↑7% ↑8%

* Single dose unless otherwise noted.

† Percent change (with/without coadministered drug and no change = 0%); ↑ and ↓ indicate the exposure increase and decrease, respectively.

‡ AUC = AUC (INF) for drugs given as single dose and AUC = AUC (TAU) for drugs given in multiple doses.

3, 4,5-triol. Its molecular formula is C21H25ClO6 and its molecular weight is 408.88. The chemical structure is:

6 Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Dapagliflozin and metformin hydrochloride extended-release tablets

In reported study 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

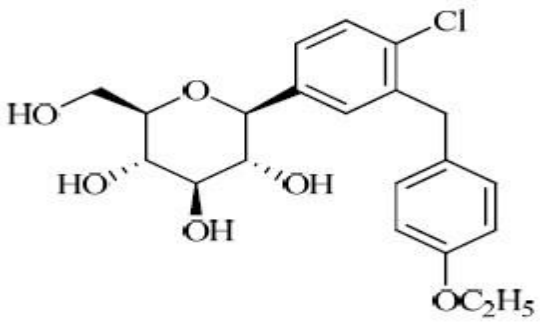
Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 and 1500 mg/kg/day, respectively. These doses are both approximately 4 times the MRHD of 2000 mg based on body surface area comparisons.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

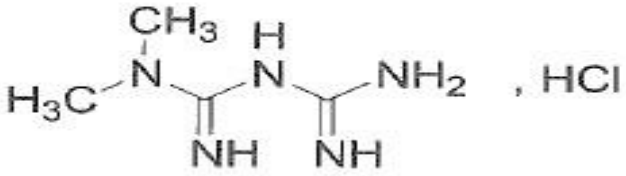
Dapagliflozin:

The chemical name of Dapagliflozin is (1S)-1,5-Anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl) methyl] phenyl]-D-glucitol(2S,3R,4R,5S,6R)-2-(3-(4 ethoxybenzyl)-4chlorophenyl)-6-hydroxymethyltetrahydro-2H-pyran- 3,4,5-triol. Its molecular formula is $C_{21}H_{25}ClO_6$ and its molecular weight is 408.88. The chemical structure is:



Metformin Hydrochloride:

The chemical name of Metformin Hydrochloride is 1,1-dimethylbiguanide hydrochloride. Its molecular formula is $C_4H_{11}N_5$, HCl and its molecular weight is 165.6. The chemical structure is:



Product Description:

GLUCRETA M 10+1000
Yellow to dark yellow, biconvex, oval-shaped, beveled edge, film-coated tablets with "C14" debossed on one side and plain on the reverse side.

GLUCRETA M 5+1000
Pink to dark pink, biconvex, oval-shaped, beveled edge, film-coated tablets with "C13" debossed on one side and plain on the reverse side.

GLUCRETA M 10+500
Pink, biconvex, capsule shaped, beveled edge, film-coated tablets with "C12" debossed on one side and plain on the reverse side.

GLUCRETA M 5+500
Orange, biconvex, capsule-shaped, beveled edge, film-coated tablets with "C11" debossed on one side and plain on the reverse side.

8 Pharmaceutical particulars

8.1 Incompatibilities
None Stated

8.2 Shelf-life
Do not use later than the date of expiry.

8.3 Packaging information
Available in blister pack of 10 Tablets.

8.4 Storage and handing instructions
Store at a temperature not exceeding 30°C, protected from light and moisture.

Keep out of reach of children.

9 Patient Counselling Information

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 9.4.

What is in this leaflet?

9.1 What GLUCRETA M are and what are they used for

Dapagliflozin and Metformin Hydrochloride Extended Release Tablets contains 2 prescription medicines called dapagliflozin and metformin 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..

•Dapagliflozin and metformin hydrochloride extended-release tablets are not for people with type 1 diabetes.

•Dapagliflozin and metformin hydrochloride extended-release tablets are not for people with diabetic ketoacidosis (increased ketones in your blood or urine).

It is not known if dapagliflozin and metformin hydrochloride extended-release tablets are safe and effective in children younger than 18 years of age.

9.2 What you need to know before you use GLUCRETA M

Who should not take GLUCRETA M

Do not take dapagliflozin and metformin hydrochloride extended-release tablets if you:

- have moderate to severe kidney problems
- Are allergic to dapagliflozin, metformin HCl, or any of the ingredients in medicine. See the end of this Medication Guide for a list of ingredients in dapagliflozin and metformin hydrochloride extended-release tablets. Symptoms of a **serious** allergic reaction to dapagliflozin and metformin hydrochloride extended-release 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 and metformin hydrochloride extended-release 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 GLUCRETA M Before you take GLUCRETA M, tell your healthcare provider if you:

- have type 1 diabetes or have had diabetic ketoacidosis
- have kidney problems
- have liver problems
- have heart problems, including congestive heart failure

- drink alcohol very often, or drink a lot of alcohol in short-term “binge” drinking Are going to get an injection of dye or contrast agents for an x-ray procedure. Medicine will need to be stopped for a short time. Talk to your healthcare provider about when you should stop dapagliflozin and metformin hydrochloride extendedrelease tablets and when you should start dapagliflozin and metformin hydrochloride extended-release tablets again.
- Are going to have surgery and will not be able to eat or drink much. Dapagliflozin and metformin hydrochloride extended-release tablets will need to be stopped for a short time. Talk to your healthcare provider about when you should stop medicine and when you should start medicine again.
- have or have had bladder cancer
- Are pregnant or plan to become pregnant. Dapagliflozin and metformin hydrochloride extended-release 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 and metformin hydrochloride extended-release tablets passes into your breast milk. Talk with your healthcare provider about the best way to feed your baby if you are taking dapagliflozin and metformin hydrochloride extended-release tablets.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Dapagliflozin and metformin hydrochloride extended-release tablets may affect the way other medicines work and other medicines may affect the way dapagliflozin and metformin hydrochloride extended-release 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 your healthcare provider and pharmacist when you get a new medicine.

Warnings and precautions

What is the most important information I should know GLUCRETA M?

Talk to your doctor before taking **GLUCRETA M if** you are suffering or have ever suffered from any of the following conditions or illnesses

GLUCRETA M can cause serious side effects, including:

- **Lactic Acidosis.** Metformin HCl, one of the medicines in dapagliflozin and metformin hydrochloride extended-release tablets, can cause a rare, but serious, side effect called lactic acidosis (a build-up of lactic acid in the blood) that can cause death. Lactic acidosis is a medical emergency and must be treated in a hospital.

Stop taking GLUCRETA M and call your healthcare provider right away if you have any of the following symptoms which could be signs of lactic acidosis:

- you feel very weak or tired
- you have unusual (not normal) muscle pain
- you have trouble breathing
- you have unusual sleepiness or sleep longer than usual
- you have stomach pains, nausea, or vomiting
- you feel dizzy or lightheaded
- you have a slow or irregular heartbeat

You have a higher chance of getting lactic acidosis with Drug. If You

- Have kidney problems or your kidneys are affected by certain x-ray tests that use injectable dye. People whose kidneys are not working properly should not take dapagliflozin and metformin hydrochloride extended-release tablets.
- have liver problems
- have congestive heart failure that requires treatment with medicines
- 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
- are 80 years of age or older and have not had your kidneys tested

9.3 How to use GLUCRETA M

Take Medicine exactly as your healthcare provider tells you to take it.

Do not change your dose of Medicine without talking to your healthcare provider.

Take Medicine 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 Medicine whole. Do not crush, cut, or chew dapagliflozin and metformin hydrochloride extended-release tablets.

You may sometimes pass a soft mass in your stools (bowel movement) that looks like medicine.

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 medicine.

Your healthcare provider may do certain blood tests before you start medicine and during your treatment.

Your healthcare provider will check your diabetes with regular blood tests, including your blood sugar levels and your A1C.

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 medicine, 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. **Do not** take 2 tablets of medicine at the same time unless your healthcare provider tells you to do so.

If you take too much medicine, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while taking GLUCRETA M?

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

9.4 Possible Side Effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some side effects can be serious and need immediate medical attention

You should see your doctor immediately if you experience any of the following symptoms.

Medicine can cause some people to have dehydration (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, lightheaded, or weak, especially when you stand up (orthostatic hypotension).

You may be at a higher risk of dehydration if you:

- have low blood pressure
- take medicines to lower your blood pressure, including water pills (diuretics)
- are 65 years of age or older
- are on a low salt diet
- have kidney problems

• • **Low blood sugar (hypoglycemia).** If you take Medicine with another medicine that can cause low blood sugar, such as sulfonylureas or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take Medicine. Signs and symptoms of low blood sugar may include:

- weakness
- headache
- confusion
- irritability
- shaking or feeling jittery
- sweating
- drowsiness
- hunger
- fast heartbeat dizziness

Kidney problems

Low vitamin B12 (vitamin B12 deficiency). Using metformin for long periods of time may cause a decrease in the amount of vitamin B12 in your blood, especially if you have

had low vitamin B12 levels before. Your healthcare provider may do blood tests to check your vitamin B12 levels.

Vaginal yeast infection. Women who take dapagliflozin and metformin hydrochloride extended-release tablets may get vaginal yeast infections. Symptoms of a vaginal yeast infection include:

- vaginal odour
- white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese)
- vaginal itching

Yeast infection of the penis (balanitis). Men who take this Medicine may get a yeast infection of the skin around the penis. Certain men who are not circumcised may have swelling of the penis that makes it difficult to pull back the skin around the tip of the penis. Other symptoms of yeast infection of the penis include:

- redness, itching, or swelling of the penis
- rash of the penis
- foul smelling discharge from the penis pain in the skin around the penis

Talk to your healthcare provider about what to do if you get symptoms of a yeast infection of the vagina or penis. Your healthcare provider may suggest you use an overthe-counter antifungal medicine. Talk to your healthcare provider right away if you use an over-the-counter antifungal medication and your symptoms do not go away.

• **increased fats in your blood (bad cholesterol or LDL)**

• • **Bladder cancer.** In studies of dapagliflozin in people with diabetes, bladder cancer occurred in a few more people who were taking dapagliflozin than in people who were taking other diabetes medications. There were too few cases to know if bladder cancer was related to dapagliflozin. You should not take dapagliflozin and metformin hydrochloride extended-release tablets if you have bladder cancer. Tell your healthcare provider right away if you have any of the following symptoms:

- blood or a red Color in your urine pain while you urinate

The most common side effects of GLUCRETA M include:

- vaginal yeast infections and yeast infections of the penis
- stuffy or runny nose and sore throat
- urinary tract infections
- diarrhea
- headache
- nausea and vomiting
- Tell your healthcare provider or pharmacist if you have any side effect that bothers you or does not go away.
- These are not all of the possible side effects of Medicine. For more information, ask your healthcare provider or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:
http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store GLUCRETA M

Keep out of the sight and reach of children.

Store at a temperature not exceeding 30°C, protected from light and moisture.

Do not use Dapagliflozin and Metformin Hydrochloride Extended Release Tablets after the expiry date which is stated on the carton or the blister after 'EXP'. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

9.6 Contents of the pack and other information

What GLUCRETA M contain:
Active ingredients: Dapagliflozin and Metformin Hydrochloride

Inactive ingredients of Dapagliflozin and Metformin Hydrochloride Extended-Release Tablets are as follow:

GLUCRETA M 10+1000
Lactose Anhydrous, Microcrystalline Cellulose, Croscarmellose Sodium, Povidone, Isopropyl alcohol, Colloidal silicon dioxide, Yellow oxide of iron, Magnesium stearate, Sodium carboxymethyl cellulose, Hypromellose, Talc, Polyvinyl alcohol, Titanium Dioxide, Macrogol/PEG.

GLUCRETA M 5+1000
Lactose anhydrous, Microcrystalline cellulose, Croscarmellose sodium, Povidone, Isopropyl alcohol, Colloidal silicon dioxide, Yellow oxide of iron, Magnesium stearate, Sodium carboxymethyl cellulose, Hypromellose, Talc, Polyvinyl alcohol, Titanium Dioxide, Macrogol/PEG, Red oxide of iron.

GLUCRETA M 10+500
Lactose anhydrous, Microcrystalline cellulose, Croscarmellose sodium, Povidone, Isopropyl alcohol, Colloidal silicon dioxide, Yellow oxide of iron, Magnesium stearate, Sodium carboxymethyl cellulose, Hypromellose, Talc, Polyvinyl alcohol, Titanium Dioxide, Macrogol/PEG, Red oxide of iron

GLUCRETA M 5+500
Lactose anhydrous, Microcrystalline cellulose, Croscarmellose sodium, Povidone, Isopropyl alcohol, Colloidal silicon dioxide, Yellow oxide of iron, Magnesium stearate, Sodium carboxymethyl cellulose, Hypromellose, Talc, Polyvinyl alcohol, Titanium Dioxide, Macrogol/PEG, Sunset Yellow FCF.

10 Details of manufacturer

Manufactured by:
Torrent Pharmaceuticals Ltd.
32 No. Middle Camp, NH-10, East District, Gangtok, Sikkim-737 135

11 Details of permission or licence number with date

M/563/2010 dated 06-dec-2021

12 Date of revision

MAY-2022

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ GLUCRETA M 5+500, 5+1000, 10+500, 10+1000 /MAY-22/03/PI