DAPAGLIFLOZIN + METFORMIN HCl

Dapiflozin M

℞ 5mg/1g, 10mg/500mg, 10mg/1g Film- Coated Tablet

Oral Hypoglycemic Agents

1. NAME OF THE MEDICINAL PRODUCT

Dapagliflozin and Metformin Hydrochloride (DAPIFLOZIN M)

2.QUALITATIVE AND QUANTITATIVE COMPOSITION

Dapagliflozin + Metformin HCl (Dapiflozin M 5/1000)

Each Film-Coated Tablet contains:
Dapagliflozin……..….5mg
Metformin hydrochloride…….....….1g
(in extended-release form)

Dapagliflozin + Metformin HCl (Dapiflozin M 10/500)

Each Film-Coated Tablet contains:
Dapagliflozin……..10mg
Metformin hydrochloride……..500mg
(in extended-release form)

Dapagliflozin + Metformin HCl (Dapiflozin M 10/1000)

Each Film-Coated Tablet contains:
Dapagliflozin……..10mg
Metformin hydrochloride.....……..1g

3.PHARMACEUTICAL FORM

Dapagliflozin + Metformin HCl (DAPIFLOZIN M 5/1000)

Brown to dark brown, biconvex, oval shaped, film coated tablets, debossed “156” on one side and plain on other side.

Dapagliflozin + Metformin HCl (DAPIFLOZIN M 10/500)

Light pink to pink, biconvex, caplet shaped, film coated tablets, debossed “155” on one side and plain on other side.

Dapagliflozin + Metformin HCl (DAPIFLOZIN M 10/1000)

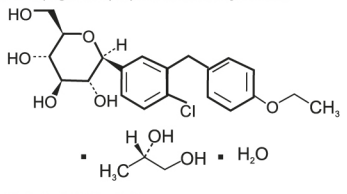
Yellow to dark yellow, biconvex, oval shaped, film coated tablets, debossed “157” on one side and plain on other side.

DESCRIPTION

Dapiflozin M tablets contain: dapagliflozin, a SGLT2 inhibitor, and metformin HCl, a biguanide.

Dapagliflozin

Dapagliflozin propanediol monohydrate is an orally-active inhibitor of the human renal sodiumglucose co-transporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin is described chemically as (1S)-1,5-Anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-D-glucitol, (S)-propylene glycol, monohydrate.
The chemical structure of dapagliflozin propanediol monohydrate is:

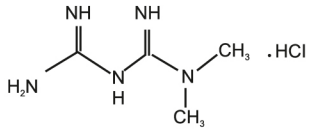


Molecular formula: $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$
Molecular weight: 502.98

Metformin hydrochloride

Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is a biguanide with antihyperglycaemic effects.

The chemical structure of metformin hydrochloride is:



Molecular formula: $C_4H_{11}N_5 \cdot HCl$
Molecular weight: 165.63

4.CLINICAL PARTICULARS

4.1.Therapeutic Indications

Dapagliflozin + Metformin HCl (Dapiflozin M) is indicated in adults for the treatment of type 2 diabetes mellitus as an adjunct to diet and exercise.

Use in Patients at Risk for Volume Depletion:

Dapagliflozin:

Due to its mechanism of action, dapagliflozin induces osmotic diuresis which may lead to the modest decrease in blood pressure observed in clinical studies (see section 5.1 Pharmacodynamic properties). For patients at risk for volume depletion due to co-existing conditions, a starting dose of dapagliflozin 5 mg once daily may be appropriate as Dapagliflozin + Metformin HCl (Dapiflozin M) or individual components. Temporary interruption of Dapagliflozin + Metformin HCl (Dapiflozin M) should be considered for patients who develop volume depletion.

Use with Medications Known to Cause Hypoglycaemia:

Dapagliflozin:

Insulin and insulin secretagogues, such as sulfonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with Dapagliflozin.

Metformin:

Hypoglycaemia 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 hypoglycaemic effects. Hypoglycaemia may be difficult to recognise in the elderly and in people who are taking betaadrenergic blocking drugs.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Post-marketing cases of necrotizing fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.
Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotizing fasciitis. If Fournier's gangrene is suspected, Dapagliflozin + Metformin HCl (Dapiflozin M) should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

4.5.Interaction with Other Medicinal Products and Other Forms of Interaction Interaction with Dapagliflozin and Metformin:

Co-administration of multiple doses of dapagliflozin and metformin did not meaningfully alter the pharmacokinetics of either dapagliflozin or metformin in healthy subjects.
There have been no formal interaction studies for Dapagliflozin + Metformin HCl (Dapiflozin M). The following statements reflect the information available on the individual active substances.

Drug Interactions with Dapagliflozin:

The metabolism of dapagliflozin is primarily mediated by UGT1A9-dependent glucuronide conjugation. The major metabolite, dapagliflozin 3-O-glucuronide, is not an SGLT2 inhibitor.
In in vitro studies, dapagliflozin and dapagliflozin 3-O-glucuronide neither inhibited CYP 1A2, 2C9, 2C19, 2D6, 3A4, nor induced CYP1A2, 2B6 or 3A4. Therefore, dapagliflozin is not expected to alter the metabolic clearance of co-administered drugs that are metabolized by these enzymes, and drugs that inhibit or induce these enzymes are not expected to alter the metabolic clearance of dapagliflozin. 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-Oglucuronide 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.

Effect of Other Drugs on Dapagliflozin:

In interaction studies conducted in healthy subjects, using mainly single dose design, the pharmacokinetics of dapagliflozin were not altered by metformin (an hOCT-1 and hOCT-2 substrate), pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate), sitagliptin (an hOAT-3 substrate and P-glycoprotein substrate), glimepiride (a CYP2C9 substrate), voglibose (an α-glucosidase inhibitor), hydrochlorothiazide, bumetanide, valsartan, or simvastatin (a CYP3A4 substrate). Therefore, meaningful interaction of dapagliflozin with other substrates of hOCT-1, hOCT-2, hOAT-3, P-gp, CYP2C8, CYPC9, CYP3A4, and other α-glucosidase inhibitor would not be expected.
Following co-administration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolizing enzymes) or mefenamic acid (an inhibitor of UGT1A9), a 22% decrease and a 51% increase, respectively, in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion in either case.
Co-administration of dapagliflozin and bumetanide did not meaningfully change the pharmacodynamic effect of dapagliflozin to increase urinary glucose excretion in healthy subjects.

Effect of Dapagliflozin on Other Drugs:

In interaction studies conducted in healthy subjects, using mainly a single dose design, dapagliflozin did not alter the pharmacokinetics of metformin, pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, simvastatin, digoxin (a P-gp substrate), or warfarin (Swarfarin is a CYP2C substrate). Therefore, dapagliflozin is not a clinical meaningful inhibitor of hOCT-1, hOCT-2, hOAT-3, P-gp transporter pathway, and CYP2C8, CYP2C9, CYP2C19 and CYP3A4 mediated metabolism.
Co-administration of dapagliflozin and bumetanide did not meaningfully alter the steady-state pharmacodynamic responses (urinary sodium excretion, urine volume) to bumetanide in healthy subjects.
Dapagliflozin did not affect the anticoagulant activity of warfarin as measured by the prothrombin time (International Normalized Ratio [INR]).

4.2.Dosage and Method of Administration

Dapagliflozin + Metformin HCl (Dapiflozin M) should be taken orally, once daily with the evening meal.

The recommended dose of dapagliflozin is 10 mg once daily. The recommended starting dose of metformin is 500 mg once daily, which can be titrated to 2000 mg once daily, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin.

In patients treated with metformin, the dose of Dapagliflozin + Metformin HCl (Dapiflozin M) should provide metformin at the dose already being taken, or the nearest therapeutically appropriate dose.

If no adequate strength of Dapagliflozin + Metformin HCl (Dapiflozin M) is available, individual mono-components should be used instead of fixed dose combination.

Patients should be informed that Dapagliflozin + Metformin HCl (Dapiflozin M) tablets must be swallowed whole and never crushed, cut, or chewed. Occasionally, the inactive ingredients of Dapagliflozin + Metformin HCl (Dapiflozin M) will be eliminated in the feces as a soft, hydrated mass that may resemble the original tablet.

Special population:

Patients with Renal Impairment:

Assess renal function prior to initiation of Dapagliflozin + Metformin HCl (Dapiflozin M) and periodically thereafter (see Special warnings and precautions for use and Pharmacokinetic properties).

Mild renal impairment:

No dose adjustment of Dapagliflozin + Metformin HCl (Dapiflozin M) is required for patients with mild renal impairment (eGFR 60-89 mL/min/1.73 m^2 by Modified Diet in Renal Disease [MDRD] eGFR equation).

Moderate Renal Impairment:

Dapagliflozin + Metformin HCl (Dapiflozin M) is not recommended for the treatment of diabetes in patents with eGFR persistently below 45 mL/min/1.73 m^2 (see Special warnings and precautions for use). No dose adjustment is required for patients with eGFR ≥ 45 mL/min/1.73 m^2.

Severe renal impairment:

Due to the metformin component, Dapagliflozin + Metformin HCl (Dapiflozin M) is contraindicated in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) (see Contraindications).

Patients with Hepatic Impairment:

Since impaired hepatic function has been associated with some cases of lactic acidosis in patients taking metformin, Dapagliflozin + Metformin HCl (Dapiflozin M) should generally be avoided in patients with clinical or laboratory evidence of hepatic impairment (see Use in Patients with Hepatic Impairment).

Pediatric and Adolescent patients:

Safety and effectiveness of Dapagliflozin + Metformin HCl (Dapiflozin M) in pediatric and adolescent patients have not been established.

Elderly patients:

Because metformin is eliminated by the kidney, and because elderly patients are more likely to have decreased renal function, Dapagliflozin + Metformin HCl (Dapiflozin M) should be used with caution as age increases. The renal function recommendations provided for all patients also apply to elderly patients. (see Special warnings and precautions for use).

Patients at Risk for Volume Depletion:

For patients at risk for volume depletion due to co-existing conditions, a 5 mg starting dose of dapagliflozin may be appropriate (see Special warnings and precautions for use and Pharmacodynamic properties).

4.3.Contraindications

Dapagliflozin + Metformin HCL is contraindicated in patients with:

Severe renal impairment (eGFR < 30 mL/min/1.73 m^2)

Metabolic acidosis

Patients with a history of any serious hypersensitivity reaction to the active substance or to any of the excipients.

4.4.Special Warnings and Special Precautions for Use

Lactic Acidosis:

Metformin Hydrochloride:

Lactic acidosis is a very rare, but serious and potentially fatal in the absence of prompt treatment, metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency, dehydration, any acute conditions associated with hypoxia or impacting renal function (see Special warnings and precautions for use).

Medicinal products that can acutely impair renal function, such as antihypertensives, diuretics and NSAIDs, should be initiated with caution in metformin-treatment patients (see Interaction with other medicinal products and other forms of interaction).

Patients and/or care-givers should be informed on the risk of lactic acidosis. Lactic acidosis is characterized by symptoms such as acidotic dyspnea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with Dapagliflozin + Metformin HCl (Dapiflozin M) should be discontinued and the patient hospitalized immediately.

Interactions between metformin hydrochloride and other drugs:

Cationic Drugs:

Cationic drugs (e.g., amiloride, 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. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of metformin and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Glyburide:

In a single-dose interaction study in type 2 diabetes patients, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and maximum concentration (C_{max}) were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects make the clinical significance of this interaction uncertain.

Furosemide:

A single-dose, metformin-furosemide drug-interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when coadministered chronically.

Nifedipine:

A single-dose, metformin-nifedipine drug-interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Use with Other Drugs:

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs 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 metformin, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving metformin, the patient should be observed closely for hypoglycemia.

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

Metformin is negligibly bound to plasma proteins and, therefore, is less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

Other Interactions:

The effects of smoking, diet, herbal products, and alcohol use on the pharmacokinetics of dapagliflozin have not been specifically studied.

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

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

4.6 Pregnancy and Lactation

Pregnancy:

Dapagliflozin + Metformin HCl (Dapiflozin M) must not be used in the second and third trimesters of pregnancy. In the time period corresponding to second and third trimester of pregnancy with respect to human renal maturation, maternal exposure to dapagliflozin in rat studies was associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny (see Preclinical Safety Data).

In conventional studies of embryo-fetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the first trimester period of non-renal organogenesis in humans. No developmental toxicities were observed in rabbits at any dose tested (1191× the maximum recommended human dose [MRHD]). In rats, dapagliflozin was neither embryolethal nor teratogenic (1441× the MRHD) in the absence of maternal toxicity.

Determination of fetal concentrations demonstrated a partial placental barrier to metformin. There are no adequate and well-controlled studies of Dapagliflozin + Metformin HCl (Dapiflozin M) in pregnant women. When pregnancy is detected, Dapagliflozin + Metformin HCl (Dapiflozin M) should be discontinued.

Use in Patients with Renal Impairment:
Dapagliflozin + Metformin HCl (Dapiflozin M) is not recommended for the treatment of diabetes in patients with eGFR persistently below 45 mL/min/1.73 m^2 as the glycemic efficacy of dapagliflozin is dependent on renal function (see Special populations). The maximum dose of metformin in patients with an eGFR of 30 to less than 45 mL/min/1.73 m^2 is 1000 mg once daily.
Due to metformin, Dapagliflozin + Metformin HCl (Dapiflozin M) is contraindicated in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) (see Contraindications).
Dapagliflozin has not been studied in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2 by MDRD) or end-stage renal disease (ESRD).
Metformin is excreted by the kidney and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function (see Lactic acidosis).
Assess renal function prior to initiation, Dapagliflozin + Metformin HCl (Dapiflozin M) and then periodically thereafter:
• at least annually
• at least two to four times a year in patients with renal function where eGFR levels are approaching 45 mL/min/1.73 m^2 and in elderly patients.

Acute Conditions Associated with Hypoxia or Impacting Renal Function:
Metformin hydrochloride
Cardiovascular collapse (shock), acute congestive heart failure, acute myocardial infarction, and other conditions characterised by hypoxemia have been associated with lactic acidosis and may also cause pre-renal azotemia. Acute conditions such as dehydration, severe infections, and hypoperfusion, have potential to alter renal function. In these situations, metformin must be discontinued.

Radiologic Studies with Intravascular Iodinated Contrast Materials:
Metformin hydrochloride:
Intravascular administration of iodinated contrast agents in radiological studies can lead to an acute decrease in renal function and has been associated with lactic acidosis in patients receiving metformin. Therefore, Dapagliflozin + Metformin HCl (Dapiflozin M) should temporarily be discontinued prior to, or at the time of the procedure and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be stable.

Surgical Procedures:
Metformin hydrochloride:
Use of Dapagliflozin + Metformin HCl (Dapiflozin M) 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 stable.

Use in Patients with Hepatic Impairment:
Metformin hydrochloride:
Since impaired hepatic function has been associated with some cases of metformin associated lactic acidosis, Dapagliflozin + Metformin HCl (Dapiflozin M) should be avoided in patients with clinical or laboratory evidence of hepatic disease.

Excessive Alcohol intake:
Metformin hydrochloride:
Alcohol potentiates the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake, while receiving Dapagliflozin + Metformin HCl (Dapiflozin M)

Ketoacidosis:
Dapagliflozin:
There have been reports of ketoacidosis, including diabetic ketoacidosis, in patients with type 1 and type 2 diabetes mellitus taking Dapagliflozin + Metformin HCl (Dapiflozin M) and other SGLT2 inhibitors. Dapagliflozin + Metformin HCl (Dapiflozin M) is not indicated for the treatment of patients with type 1 diabetes mellitus.
Patients treated with Dapagliflozin + Metformin HCl (Dapiflozin M)who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/l (250 mg/dl). If ketoacidosis is suspected, discontinuation or temporary interruption of Dapagliflozin + Metformin HCl (Dapiflozin M) should be considered and the patient should be promptly evaluated.
Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), insulin dose reduction, reduced caloric intake or increased insulin requirements due to infections, illness or surgery and alcohol abuse. Dapagliflozin + Metformin HCl (Dapiflozin M) should be used with caution in these patients.

Change in Clinical Status of Patients with Previously Controlled Type 2 Diabetes:
Metformin hydrochloride:
Patient with type 2 diabetes previously well controlled on Dapagliflozin + Metformin HCl (Dapiflozin M) 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 + Metformin HCl (Dapiflozin M) must be stopped immediately and other appropriate corrective measures initiated.

Lactation:
Dapagliflozin + Metformin HCl (Dapiflozin M) must not be used by a nursing woman.
No studies in lactating animals have been conducted with the combined components of Dapagliflozin + Metformin HCl (Dapiflozin M) In studies performed with the individual components, both dapagliflozin and metformin are excreted in the milk of lactating rats.
Direct and indirect exposure of dapagliflozin to weanling juvenile rats and during late pregnancy are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny, although the long-term functional consequences of these effects are unknown. These periods of exposure coincide with a critical window of renal maturation in rats. As functional maturation of the kidneys in humans continues in the first 2 years of life, dapagliflozin-associated dilated renal pelvis and tubules noted in juvenile rats could constitute potential risk for human renal maturation during the first 2 years of life. Additionally, the negative effects on body-weight gain associated with lactational exposure in weanling juvenile rats suggest that dapagliflozin must be avoided during the first 2 years of life (see Preclinical Safety Data).

It is not known whether dapagliflozin or metformin are secreted in human milk.

4.7.Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

4.8.Adverse Drug Reactions
Dapagliflozin + Metformin:
Data from a pre-specified pool of patients from 8 short-term, placebo-controlled studies of dapagliflozin co-administered with metformin immediate- or extended-release was used to evaluate safety data. This pool included several add-on studies (metformin alone and in combination with a DPP4 inhibitor and metformin, or insulin and metformin, 2 initial combination with metformin studies, and 2 studies of patients with cardiovascular disease (CVD) and type 2 diabetes who received their usual treatment (with metformin as background therapy). For studies that included background therapy with and without metformin, only patients who received metformin were included in the 8-study placebo-controlled pool. Across these 8 studies 983 patients were treated once daily with dapagliflozin 10 mg and metformin and 1185 were treated with placebo and metformin. These 8 studies provide a mean duration of exposure of 23 weeks. The mean age of the population was 57 years and 2% were older than 75 years. Fifty-four percent (54%) of the population was male; 88% White, 6% Asian, and 3% Black or African American. At baseline, the population had diabetes for an average of 8 years, mean hemoglobin A1c (HbA1c) was 8.4%, and renal function was normal or mildly impaired in 90% of patients and moderately impaired in 10% of patients.

Dapagliflozin:
The safety profile of dapagliflozin in type 2 diabetes mellitus has been evaluated in clinical studies including more than 15000 subjects treated with dapagliflozin. For further information about the clinical studies, see Pharmacodynamic properties.
The incidence of adverse reactions was determined using a pre-specified pool of patients from 13 short-term (mean duration 22 weeks), placebo-controlled studies in type 2 diabetes. Across these 13 studies, 2360 patients were treated once daily with dapagliflozin 10 mg and 2295 were treated with placebo (either as monotherapy or in combination with other antidiabetic therapies).
Additionally, dapagliflozin 5 mg was evaluated in a 12-study, short-term, placebo-controlled pool of patients that included 1145 patients treated with dapagliflozin 5 mg (mean exposure = 22 weeks) and 1393 patients treated with (mean exposure = 21 weeks), either as monotherapy or in combination with other antidiabetic therapies.

In the dedicated cardiovascular (CV) outcomes study in patients with type 2 diabetes mellitus, 8574 patients received dapagliflozin 10 mg and 8569 received placebo for a median exposure time of 48 months. In total, there were 30623 patient-years of exposure to dapagliflozin.

Adverse reactions
The adverse reactions in patients treated with dapagliflozin 10 mg with and without metformin in clinical trials in type 2 diabetes mellitus and postmarketing are shown in Table 1.

Table 1: Adverse Drug Reactions by Frequency and System Organ Class (SOC)

System Organ Class	Common	Rare	Unknown
Infections and Infestations	Genital infection[a,b] Urinary tract infection[a,c]		Necrotizing Fasciitis of the perineum Fournier's Gangrene)[i]
Metabolism and Nutrition Disorders		Diabetic ketoacidosis[f]	
Skin and subcutaneous tissue disorders			Rash[g,h]
Musculoskeletal and Connective Tissue Disorders	Back pain[d]		
Renal Urinary Disorders	Pollakiuria[a] and polyuria[a,e]		

[a] Identified from 8 placebo-controlled studies, including 2 initial combination with metformin, 2 add-on to metformin, 1 add-on to insulin, 1 add-on to sitagliptin, and 2 studies with combination add-on therapy.

[b] Multiple adverse events terms, including vulvovaginal infections and candidiasis, balanoposthitis, balanitis candida, penile abscess, penile infection, vulval abscess and vaginitis bacterial.

[c] Multiple adverse event terms, including genitourinary tract infection, cystitis, pyelonephritis, trigonitis, urethritis and prostatitis.

[d] Additional events identified from 13 placebo-controlled studies with dapagliflozin 10 mg in type 2 diabetes mellitus including 3 monotherapy, 1 initial combination with metformin, 2 add- on to metformin, 2 add-on to insulin, 1 add-on to pioglitazone, 1 add-on to sitagliptin, 1 add-on to glimepiride, and 2 studies with combination add-on therapy.

[e] Represents multiple adverse events terms, including polyuria, urine output increased.

[f] Identified from the cardiovascular outcomes study in patients with type 2 diabetes. Frequency is based on annual rate.

[g] Identified during postmarketed use of dapagliflozin. Because these reactions are reported voluntarily from a population of an uncertain size, it is not always possible to reliably estimate their frequency.

[h] Rash includes the following preferred terms, listed in order of frequency in clinical trials: Rash, Rash generalized, Rash pruritic, Rash macular, Rash maculo-papular, Rash pustular, Rash vesicular, Rash erythematous. In active- and placebocontrolled clinical trials (Dapagliflozin, N=5936, All control, N=3403), the frequency of Rash was similar for Dapagliflozin (1.4%) and All control (1.4%), respectively, corresponding to the frequency ''Common".

[i] See Necrotizing fasciitis of the perineum (Fournier's gangrene).

Description of selected adverse reactions:

Genital Infections:

Events of genital infections were reported in 5.5% and 0.6% of patients who received dapagliflozin 10 mg and placebo, respectively, in the 13-study, short-term, placebo-controlled pool. The events of genital infections reported in patients treated with dapagliflozin 10 mg were all mild to moderate.Most events of genital infection responded to an initial course of standard treatment and rarely resulted in discontinuation from the study (0.2% dapagliflozin 10 mg vs 0% in placebo). Infections were reported more frequently in females (8.4% dapagliflozin 10 mg vs 1.2% placebo) than in males (3.4% dapagliflozin 10 mg vs 0.2% placebo). The most frequently reported genital infections were vulvovaginal mycotic infections in females, and balanitis in males.

In the CV outcomes study, the number of patients with serious adverse events (SAE) of genital infections were few and balanced: 2 (<0.1%) patients in each of the dapagliflozin and placebo groups.

Urinary Tract Infections:

Events of urinary tract infections (UTI) were reported in 4.7% and 3.5% of patients who received dapagliflozin 10 mg and placebo, respectively, in the 13-study, short-term, placebo-controlled pool. Most events of urinary tract infections reported in patients treated with dapagliflozin 10 mg were mild to moderate. Most patients responded to an initial course of standard treatment, and urinary tract infections rarely caused discontinuation from the study (0.2% dapagliflozin 10 mg vs 0.1% placebo). Infections were more frequently reported in females (8.5% dapagliflozin 10 mg vs 6.7% placebo) than in males (1.8% dapagliflozin 10 mg vs 1.3% placebo).

In the CV outcomes study there were fewer patients with SAEs of UTI in the dapagliflozin group compared with the placebo group: 79 (0.9%) and 109 (1.3%), respectively.

Diabetic ketoacidosis (DKA):

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

4.9.Overdosage and Treatment

Dapagliflozin

Orally-administered dapagliflozin has been shown to be safe and well-tolerated in healthy subjects at single doses up to 500 mg (50 times the MRHD). These subjects had detectable glucose in the urine for a dose-related period of time (at least 5 days for the 500 mg dose), with no reports of dehydration, hypotension, or electrolyte imbalance, and with no clinically meaningful effect on QTc interval. The incidence of hypoglycaemia was similar to placebo. In clinical studies where once-daily doses of up to 100 mg (10 times the MRHD) were administered for 2 weeks in healthy subjects and patients with type 2 diabetes, the incidence of hypoglycaemia was slightly higher than placebo and was not dose-related. Rates of adverse events including dehydration or hypotension were similar to placebo, and there were no clinically meaningful dose-related changes in laboratory parameters including serum electrolytes and biomarkers of renal function.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patients clinical status. The removal of dapagliflozin by hemodialysis has not been studied.

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.

Special Populations:

Renal Impairment:

Dapagliflozin:

For dosing recommendations for patients with moderate to severe renal impairment see Dosage and method of administration. At steady-state (20 mg once-daily dapagliflozin for 7 days), patients with type 2 diabetes and mild, moderate or severe renal impairment (as determined by iohexol clearance) had mean systemic exposures of dapagliflozin that were 32%, 60% and 87% higher, respectively, than those of patients with type 2 diabetes and normal renal function. At dapagliflozin 20 mg once-daily, higher systemic exposure to dapagliflozin in patients with type 2 diabetes mellitus and renal impairment did not result in a correspondingly higher renal-glucose clearance or 24-hour glucose excretion. The renal-glucose clearance and 24-hour glucose excretion was lower in patients with moderate or severe renal impairment as compared to patients with normal and mild renal impairment. The steady-state 24-hour urinary glucose excretion was highly dependent on renal function and 85, 52, 18, and 11 g of glucose/day was excreted by patients with type 2 diabetes mellitus and normal renal function or mild, moderate, or severe renal impairment, respectively. There were no differences in the protein binding of dapagliflozin between renal impairment groups or compared to healthy subjects. The impact of hemodialysis on dapagliflozin exposure is not known.

Metformin hydrochloride:

In patients with renal impairment, the plasma and blood half-life of metformin is prolonged in proportion to the decrease in renal function.

Hepatic Impairment:

Dapagliflozin:

For dosing recommendations for patients with moderate or severe hepatic impairment see Dosage and method of administration. A single dose (10 mg) dapagliflozin clinical pharmacology study was conducted in patients with mild, moderate or severe hepatic impairment (Child-Pugh classes A, B, and C, respectively) and healthy matched controls in order to comparethe pharmacokinetic characteristics of dapagliflozin between these populations. There were no differences in the protein binding of dapagliflozin between patients with hepatic impairment compared to healthy subjects. In patients with mild or moderate hepatic impairment mean C_{max} and AUC of dapagliflozin were up to 12% and 36% higher, respectively, compared to healthy matched control subjects. These differences were not considered to be clinically meaningful and no dose adjustment from the proposed usual dose of 10 mg once daily for dapagliflozin is proposed for these populations. In patients with severe hepatic impairment (Child-Pugh class C), mean C_{max} and AUC of dapagliflozin were up to 40% and 67% higher than matched healthy controls, respectively. No dose adjustment is required for patients with severe hepatic impairment. However, the benefit:risk for the use of dapagliflozin in patients with severe hepatic impairment should be individually assessed since the safety and efficacy of dapagliflozin have not been specifically studied in this population.

Metformin hydrochloride:

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

Age:

Dapagliflozin:

No dosage adjustment for dapagliflozin from the dose of 10 mg once daily is recommended on the basis of age. The effect of age (young: ≥18 to <40 years [n=105] and elderly: ≥65 years [n=224]) was evaluated as a covariate in a population pharmacokinetic model and compared to patients ≥40 to <65 years using data from healthy subject and patient studies). The mean dapagliflozin systemic exposure (AUC) in young patients was estimated to be 10.4% lower than in the reference group (90% CI: 87.9, 92.2%) and 25% higher in elderly patients compared to the reference group (90% CI: 123, 129%). These differences in systemic exposure were considered to not be clinically meaningful.

Metformin hydrochloride:

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function.

Pediatric and Adolescent:

Dapagliflozin:

Pharmacokinetics in the pediatric and adolescent population have not been studied.

Metformin hydrochloride:

After administration of a single oral metformin 500 mg tablet with food, geometric mean metformin C_{max} and AUC differed less than 5% between pediatric type 2 diabetic patients (12-16 years of age) and gender- and weight-matched healthy adults (20-45 years of age), all with normal renal function.

Metformin hydrochloride
High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in a hospital. The most effective method to remove lactate and metformin is haemodialysis. Events of hypoglycaemia have been reported with overdoses of metformin, although a causal association has not been established.

5.PHARMACOLOGICAL PROPERTIES
Mechanism of Action:
Dapagliflozin + Metformin HCl (Dapiflozin M) combines two anti-hyperglycaemic agents with complementary mechanisms of action to improve both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) in patients with type 2 diabetes: dapagliflozin, a SGLT2 inhibitor, and metformin hydrochloride, a member of the biguanide class.

Dapagliflozin
Dapagliflozin is a highly potent, selective, and reversible inhibitor of sodium glucose cotransporter 2 (SGLT2) that improves glycemic control in patients with type 2 diabetes mellitus by reducing renal glucose reabsorption leading to urinary excretion of excess glucose (glucuresis).
SGLT2 is selectively expressed in the kidney with no expression detected in more than 70 other tissues including liver, skeletal muscle, adipose tissue, breast, bladder, and brain. SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Despite the presence of hyperglycemia in type 2 diabetes mellitus, reabsorption of filtered glucose continues. Dapagliflozin reduces maximum tubular glucose transport by 55% and reduces renal glucose reabsorption such that glucose appears in the urine at normal plasma glucose levels. Thus, dapagliflozin improves both fasting and postprandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary excretion of excess glucose. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24-hour dosing interval, and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Thus, in healthy subjects with normal glucose, dapagliflozin has a low propensity to cause hypoglycemia. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycemia. Dapagliflozin acts independently of insulin secretion and insulin action. Over time, improvement in beta-cell function (HOMA-2) has been observed in clinical studies with dapagliflozin.
Urinary glucose excretion (glucuresis) induced by dapagliflozin is associated with caloric loss and reduction in weight. The majority of the weight reduction is body fat loss, including visceral fat rather than lean tissue or fluid loss as demonstrated by dual energy X-ray absorptiometry (DXA) and magnetic resonance imaging. Inhibition of glucose and sodium co-transport by dapagliflozin is also associated with mild diuresis and transient natriuresis.
Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is greater than 1400 times more selective for SGLT2 versus SGLT1, the major transporter in the gut responsible for glucose absorption.

Metformin hydrochloride
Metformin is an antihyperglycaemic agent which 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 utilisation. Unlike sulfonylureas, metformin does not produce hypoglycaemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see section 4.4 Special Warnings and Precautions for Use) and does not cause hyperinsulinaemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

5.1.Pharmacodynamic properties
General
Dapagliflozin
Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following the administration of dapagliflozin (Figure 1). Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day) at a dapagliflozin dose of 10 mg/day in patients with type 2 diabetes mellitus for 12 weeks. This glucose elimination rate approached the maximum glucose excretion observed at 20 mg/day of dapagliflozin. Evidence of sustained glucose excretion was seen in patients with type 2 diabetes mellitus given dapagliflozin 10 mg/day for up to 2 years.
This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume. Urinary volume increases in patients with type 2 diabetes mellitus treated with dapagliflozin 10 mg were sustained at 12 weeks and amounted to approximately 375 mL/day. The increase in urinary volume was associated with a small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations.
Urinary uric acid excretion was also increased transiently (for 3-7 days) and accompanied by a reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations ranged from 0.33 mg/dL to 0.87 mg/dL.

Gender:
Dapagliflozin:
No dosage adjustment from the dose of 10 mg once daily is recommended for dapagliflozin on the basis of gender. Gender was evaluated as a covariate in a population pharmacokinetic model using data from healthy subject and patient studies. The mean dapagliflozin AUCSS in females (n=619) was estimated to be 22% higher than in males (n=634), (90% CI: 117,124).

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

Race:
Dapagliflozin:
No dosage adjustment from the dapagliflozin dose of 10 mg once daily is recommended on the basis of race. Race (White, Black, or Asian) was evaluated as a covariate in a population pharmacokinetic model using data from healthy subject and patient studies. Differences in systemic exposures between these races were small. Compared to Whites (n=1147), Asian subjects (n=47) had no difference in estimated mean dapagliflozin systemic exposures (90% CI range 3.7% lower, 1% higher). Compared to Whites, Black subjects (n=43) had 4.9% lower estimated mean dapagliflozin systemic exposures [90% CI range 7.7% lower, 3.7% lower).

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

Body Weight:
No dose adjustments from the proposed dapagliflozin dose of 10 mg once daily is recommended on the basis of weight.
In a population pharmacokinetic analysis using data from healthy subject and patient studies, systemic exposures in high-body-weight subjects (≥120 kg, n=91) were estimated to be 78.3% (90% CI: 78.2, 83.2%) of those of reference subjects with body weight between 75 and 100 kg. This difference is considered to be small, therefore, no dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in type 2 diabetes mellitus patients with high body weight (≥120 kg) is recommended.
Subjects with low body weights (<50 kg) were not well represented in the healthy subject and patient studies used in the population pharmacokinetic analysis. Therefore, dapagliflozinsystemic exposures were simulated with a large number of subjects. The simulated mean dapagliflozin systemic exposures in low-body-weight subjects were estimated to be 29% higher than subjects with the reference group body weight. This difference is considered to be small, and based on these findings no dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in type 2 diabetes mellitus patients with low body weight (<50 kg) is recommended.

6.PHARMACEUTICAL PROPERTIES
6.1.List of Excipients
Dapagliflozin + Metformin HCl (Dapiflozin M 5/1000)
Microcrystalline Cellulose, Acetone, Anhydrous Lactose, Sepitrap 80, Croscarmellose sodium, Hypromellose, Magnesium stearate, Colloidal silicon dioxide, Sodium stearyl fumarate, Ferric Oxide Red, Opadry II brown 85F565227, Purified Water

Dapagliflozin + Metformin HCl (Dapiflozin M 10/500)
Microcrystalline Cellulose, Acetone, Anhydrous Lactose, Sepitrap 80, Croscarmellose sodium, Hypromellose, Magnesium stearate, Colloidal silicon dioxide, Sodium stearyl fumarate, Ferric Oxide Red, Opadry II orange 85F540330, Purified Water

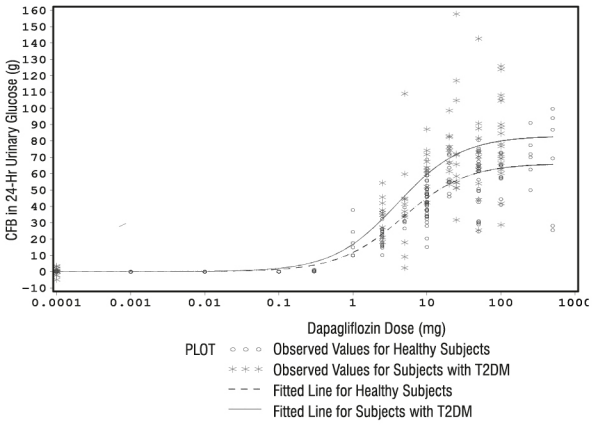
Dapagliflozin + Metformin HCl (Dapiflozin M 10/1000)
Microcrystalline Cellulose, Acetone, Anhydrous Lactose, Sepitrap 80, Croscarmellose sodium, Hypromellose, Magnesium stearate, Colloidal silicon dioxide, Sodium stearyl fumarate, Ferric Oxide Red, Opadry II yellow 85F520196, Purified Water

6.2.Incompatibilities
Not applicable.

6.3. Storage
Store at a temperatures not exceeding 30°C. Keep out of reach of children.

6.4. Special Instructions for Use, Handling, and Disposal
Not Applicable

Figure 1: Scatter Plot and Fitted Line of Change from Baseline in 24-hr Urinary Glucose Amount vs Dapagliflozin Dose in Healthy Subjects and Subjects with 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.

5.2 Pharmacokinetics

Dapagliflozin + Metformin HCl (Dapiflozin M) tablets are considered to be bioequivalent to co-administration of corresponding doses of dapagliflozin and metformin hydrochloride extended release administered together as individual tablets.

Interaction with Food

The administration of Dapagliflozin + Metformin HCl (Dapiflozin M) in healthy subjects after a standard meal compared to the fasted state results in the same extent of exposure for both dapagliflozin and metformin XR. Compared to the fasted state, the standard meal results in 5% 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.

Absorption

Dapagliflozin

Dapagliflozin was rapidly and well absorbed after oral administration and can be administered with or without food. Maximum dapagliflozin plasma concentrations (C_{max}) were usually attained within 2 hours after administration in the fasted state. The C_{max} and AUC values increased proportional to the increment in dapagliflozin dose. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%.

Metformin hydrochloride

Following a single oral dose of metformin extended-release, C_{max} is achieved with a median value of 7 hours and a range of 4 to 8 hours. At steady state, the AUC and C_{max} are less than dose proportional for metformin extended-release within the range of 500 to 2000 mg administered once daily. Peak plasma levels are approximately 0.6, 1.1, 1.4, and 1.8 μg/mL for 500, 1000, 1500, and 2000 mg once-daily doses, respectively.

Distribution:

Dapagliflozin

Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (e.g., 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, most likely as a function of time.

Metabolism:

Dapagliflozin

Dapagliflozin is a C-linked glucoside, meaning the aglycone component is attached to glucose by a carbon-carbon bond, thereby conferring stability against glucosidase enzymes. The mean plasma terminal half-life ($t_{1/2}$) for dapagliflozin is 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. Dapagliflozin is extensively metabolized primarily to yield dapagliflozin 3-Oglucuronide, which is an inactive metabolite. Dapagliflozin 3-O- glucuronide accounts for 61% of a 50 mg [^{14}C]-dapagliflozin dose and is the predominant drug- related component in human plasma, accounting for 42% (based on AUC [0-12 h]) of total plasma radioactivity, similar to the 39% contribution by parent drug. Based on AUC, no other metabolite accounts for >5% of the total plasma radioactivity. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucoselowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP mediated metabolism is a minor clearance pathway in humans.

Metformin hydrochloride

Intravenous single-dose studies in normal 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 urinary excretion, of which less than 2% is unchanged dapagliflozin. After oral administration of 50 mg [^{14}C]-dapagliflozin dose, 96% was recovered, 75% in urine and 21% in faeces. In faeces, approximately 15% of the dose was excreted as parent drug.

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,

6.5.Availability

Alu-Alu Blister Pack x 10's (Box of 30's)

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription

ADR Reporting Statement:

For suspected adverse drug reaction, report to the FDA: **www.fda.gov.ph .**
Seek medical attention immediately at the first sign of any adverse drug reaction

Manufactured by :
INVENTIA HEALTHCARE LIMITED
F1-F1/1-F75/1, Additional Ambernath M.I.D.C.,
Ambernath (East), Thane 421506, Maharashtra State, India.

Manufactured for:
MEGA LIFESCIENCES (AUSTRALIA) PTY. LTD.
60 National Avenue, Pakenham, Victoria 3810, Australia.

MEGA We care

Imported by:
MEGA LIFESCIENCES LIMITED INC.
Unit 5B 5/F BA Lepanto Bldg., 8747 Paseo de Roxas,
Bel-Air, Makati City, Metro Manila, Philippines.

Distributed by:
METRO DRUG, INC.
Sta. Rosa Estate, Barangay Macabling,
Santa Rosa, Laguna, Philippines.

DRP-16935 - Dapagliflozin + Metformin HCl (Dapiflozin M 5/1000)
DRP-16934 - Dapagliflozin + Metformin HCl (Dapiflozin M 10/500)
DRP-16933 - Dapagliflozin + Metformin HCl (Dapiflozin M 10/1000)

DATE OF FIRST AUTHORIZATION
27 August 2025

DATE OF REVISION OF PACK INSERT
September 2025