PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]Auro-Dapagliflozin / Metformin

Dapagliflozin and Metformin hydrochloride tablets

Tablets, 5 mg dapagliflozin and 850 mg metformin hydrochloride 5 mg dapagliflozin and 1000 mg metformin hydrochloride, Oral use

Combination of oral blood glucose lowering drugs

Auro Pharma Inc.
3700 Steeles Avenue West, Suite # 402
Woodbridge, Ontario, L4L 8K8,
Canada

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Auro-Dapagliflozin / Metformin (dapagliflozin / metformin hydrochloride tablets) is indicated for:

- use as an adjunct to diet and exercise in adults with type 2 diabetes mellitus who are already being treated with dapagliflozin and metformin as separate tablets and achieving glycemic control. See 14 CLINICAL TRIALS.

- use in combination with a sulfonylurea as an adjunct to diet and exercise in adults with type 2 diabetes mellitus who are already achieving glycemic control with dapagliflozin, metformin and a sulfonylurea. See 14 CLINICAL TRIALS.

- use in combination with sitagliptin as an adjunct to diet and exercise in adults with type 2 diabetes mellitus who are already achieving glycemic control with dapagliflozin, metformin and sitagliptin. See 14 CLINICAL TRIALS.

- use in combination with insulin as an adjunct to diet and exercise in adults with type 2 diabetes mellitus who are already achieving glycemic control with dapagliflozin, metformin and insulin. See 14 CLINICAL TRIALS.

1.1 Pediatrics

Pediatrics (<18 years of age): Auro-Dapagliflozin / Metformin should not be used in pediatric patients. Safety and efficacy of dapagliflozin and metformin hydrochloride tablets have not been established in patients under 18 years of age; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥65 years of age): Auro-Dapagliflozin / Metformin should be used with caution in this population as a higher proportion of patients ≥65 years of age treated with dapagliflozin had adverse reactions related to volume depletion and renal impairment or failure, compared to patients treated with placebo.

Metformin is eliminated by the kidney, and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, Auro-Dapagliflozin / Metformin is contraindicated in patients with severe renal impairment (estimated glomerular filtration rate (eGFR) <30 mL / min / 1.73 m^2). See Renal. As aging is associated with reduced renal function, Auro-Dapagliflozin / Metformin treatment should not be initiated in patients older than 80 years of age, unless their renal function is not significantly reduced. In patients with advanced age, Auro-Dapagliflozin / Metformin should be carefully titrated to establish the minimum dose

for adequate glycemic effect. More careful and frequent monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis. See 4.1 Dosing Considerations, 4.2 Recommended Dose and Dosage Adjustment, Endocrine and Metabolism, Lactic Acidosis, 7.1.4 Geriatrics.

2 CONTRAINDICATIONS

Auro-Dapagliflozin / Metformin is contraindicated in patients:

- With unstable and / or insulin-dependent (Type I) diabetes mellitus.
- With acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma, history of ketoacidosis with or without coma.
- With a history of lactic acidosis, irrespective of precipitating factors.
- With severe renal impairment (eGFR <30 mL / min / 1.73 m^2), end-stage renal disease or patients on dialysis. See Renal.
- With excessive alcohol intake, acute or chronic.
- With clinical or laboratory evidence of hepatic disease. Severe hepatic dysfunction has been associated with cases of lactic acidosis. See Hepatic/Biliary/Pancreatic.
- In cases of cardiovascular collapse and in disease states associated with hypoxemia such as cardiorespiratory insufficiency, which are often associated with hyperlactacidemia.
- During stress conditions, such as severe infections, trauma or surgery and the recovery phase thereafter.
- With severe dehydration.
- Who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- During pregnancy and breastfeeding. See 7.1 Special Populations.
- Undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function. Auro-Dapagliflozin / Metformin should be temporarily discontinued during the period around administration of iodinated contrast materials. See Renal.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Lactic Acidosis

- Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with Auro-Dapagliflozin / Metformin. See Endocrine and Metabolism, Lactic Acidosis.
- Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking Auro-Dapagliflozin / Metformin, since alcohol intake potentiates the effect of metformin on lactate metabolism. See Endocrine and Metabolism, Lactic Acidosis.

Diabetic Ketoacidosis

- Clinical trial and post-market cases of diabetic ketoacidosis (DKA), a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with type 2 diabetes mellitus (T2DM) treated with dapagliflozin and other sodium-glucose co- transporter 2 (SGLT2) inhibitors. A number of these cases have been atypical with blood glucose values below 13.9 mmol / L (250 mg / dL). Some cases of DKA have been fatal. See 8 ADVERSE REACTIONS
- Patients should be assessed for diabetic ketoacidosis immediately if non-specific symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, anorexia, excessive thirst and unusual fatigue or sleepiness occur, regardless of blood glucose level. If DKA is suspected or diagnosed, Auro-Dapagliflozin / Metformin should be **discontinued immediately**.
- Auro-Dapagliflozin / Metformin is contraindicated for the treatment of DKA or in patients with a history of DKA.
- Auro-Dapagliflozin / Metformin is contraindicated in patients with type 1 diabetes. See 2 CONTRAINDICATIONS

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Concomitant use with insulin or an insulin secretagogue (e.g., sulfonylurea): When dapagliflozin is used as add-on therapy with insulin or an insulin secretagogue (e.g., sulfonylurea), a lower dose of insulin or an insulin secretagogue may be necessary to reduce the risk of hypoglycemia. See 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS.

- Assess renal function prior to initiation of Auro-Dapagliflozin / Metformin therapy and regularly thereafter in patients with normal renal function, and more frequently in patients with renal impairment (eGFR<60 mL / min / 1.73 m^2). See Renal.
- Assess volume status and, if necessary, correct volume depletion prior to initiation of Auro-Dapagliflozin / Metformin therapy. See Cardiovascular.

Temporary interruption for surgery: Auro-Dapagliflozin / Metformin treatment should be interrupted for a minimum of 3 days, when possible, prior to major surgical procedures or procedures associated with prolonged fasting. Monitor for DKA in the post-procedural period. Ensure risk factors for ketoacidosis are resolved and that the patient is clinically stable and has resumed oral intake before considering Auro-Dapagliflozin / Metformin treatment re-initiation. See Endocrine and Metabolism.

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of Auro-Dapagliflozin / Metformin is one tablet twice daily with meals.

Each tablet is a fixed dose of dapagliflozin and metformin. Patients switching from separate tablets of dapagliflozin (10 mg total daily dose) and metformin to Auro-Dapagliflozin / Metformin should receive the same daily dose of dapagliflozin and metformin already being taken or the nearest therapeutically appropriate dose of metformin. The maximum daily dose is 10 mg dapagliflozin and 2000 mg metformin. The maximum daily dose of metformin in patients with an eGFR ≥30 mL / min / 1.73 m^2 to <45 mL / min / 1.73 m^2 is 1000 mg.

The following dosage strengths are available:

- 5 mg dapagliflozin / 850 mg metformin hydrochloride
- 5 mg dapagliflozin / 1000 mg metformin hydrochloride

Considerations for Special Populations

Pediatrics (<18 years of age): Safety and effectiveness of dapagliflozin and metformin hydrochloride in pediatric patients have not been established. Therefore, Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥65 years of age): Auro-Dapagliflozin / Metformin should be used with caution as age increases because metformin is eliminated in part by the kidney, and elderly patients are more likely to have decreased renal function associated with aging and the risk of developing lactic acidosis.

In elderly patients, the initial and maintenance dose should be conservative, and any dose adjustment should be based on careful assessment of renal function. Renal function should be monitored more frequently and generally, patients should not be titrated to the maximum dose.

See 7.1.4 Geriatrics.

Renal impairment: The glucose-lowering efficacy of dapagliflozin is dependent on renal function and declines with decreasing renal function. Monitoring of renal function is required prior to initiation of Auro-Dapagliflozin / Metformin therapy and regularly thereafter. In patients with eGFR <60 mL / min / 1.73 m^2, more frequent monitoring of renal dysfunction is recommended. No dose adjustment is required with an eGFR >45 mL / min / 1.73 m^2. See Renal.

The maximum dose of metformin in patients with an eGFR 30-<45 mL / min / 1.73 m^2 is 1000 mg daily.

Auro-Dapagliflozin / Metformin is contraindicated in patients with severe renal impairment (eGFR <30 mL / min / 1.73 m^2), end-stage renal disease or patients on dialysis.

See 2 CONTRAINDICATIONS.

Hepatic impairment: Auro-Dapagliflozin / Metformin is contraindicated in patients with severe hepatic dysfunction and should not be used in patients with clinical or laboratory evidence of hepatic disease. See 2 CONTRAINDICATIONS. Dapagliflozin exposure is increased in patients with severe hepatic impairment. See 10.3 Pharmacokinetics. Metformin use in patients with impaired hepatic function has been associated with some cases of lactic acidosis. See 7 WARNINGS AND PRECAUTIONS.

4.4 Administration

To minimize gastric intolerance for metformin component in Auro-Dapagliflozin / Metformin such as nausea and vomiting, Auro-Dapagliflozin / Metformin tablets should be taken orally with meals and should be taken whole, with a glass of water. Do not break or crush tablets.

4.5 Missed Dose

If a dose of Auro-Dapagliflozin / Metformin is missed, the patient should wait for the next dose at the usual time. A double dose of Auro-Dapagliflozin / Metformin should not be taken on the same day.

5 OVERDOSAGE

Dapagliflozin

It is 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

Available information concerning treatment of a massive overdosage of metformin hydrochloride is very limited. It would be expected that adverse reactions of a more intense character including epigastric discomfort, nausea and vomiting followed by diarrhea, drowsiness, weakness, dizziness, malaise and headache might be seen. Should those symptoms persist, lactic acidosis should be excluded. The drug should be discontinued and proper supportive therapy instituted.

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 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 Endocrine and Metabolism. 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	All Non-medicinal Ingredients
Oral	Tablet 5 mg / 850 mg 5 mg / 1000 mg	Lactose monohydrate, Hydroxy propylcellulose and Magnesium stearate **For 5mg / 850mg film coating contains:** Opadry AMB II High Performance Moisture Barrier Film Coating 88A570010 Beige. **For 5mg / 1000mg film coating contains:** Opadry AMB II High Performance Moisture Barrier Film Coating 88A520050 Yellow.

Auro-Dapagliflozin / Metformin (dapagliflozin / metformin hydrochloride) is available for oral administration as immediate release tablets containing dapagliflozin and metformin hydrochloride in the following formats:

Auro-Dapagliflozin / Metformin (dapagliflozin / metformin hydrochloride) 5 mg / 850 mg tablets are light brown to brown, oval-shaped, approximately 20.1 × 9.6 mm, film-coated tablets, debossed with “5” on one side and “850” on other side.

Auro-Dapagliflozin / Metformin (dapagliflozin / metformin hydrochloride) 5 mg / 1000 mg tablets are yellow to dark yellow, oval-shaped, approximately 21.6 × 10.6, film-coated tablets, debossed with “5” on one side and “1000” on other side.

Auro-Dapagliflozin / Metformin tablets are provided in 6x10’s of blister carton and 60’s, 100’s and 500’s HDPE bottle containers for both strengths.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Cardiovascular

Dapagliflozin

Use in patients at risk for volume depletion, hypotension and / or electrolyte imbalances: Due to its mechanism of action, dapagliflozin causes osmotic diuresis that may be associated with decreases in blood pressure, which may be more pronounced in patients with high blood glucose concentrations.

Dapagliflozin is not recommended for use in patients who are volume depleted.

Caution should be exercised in patients for whom a dapagliflozin induced drop in blood pressure could pose a risk, such as elderly patients, patients with low systolic blood pressure or moderate renal impairment, or in case of intercurrent conditions that may lead to volume depletion (such as gastrointestinal illness).

Careful monitoring of volume status is recommended. Temporary interruption of Auro-Dapagliflozin / Metformin should be considered for patients who develop volume depletion until the depletion is corrected. See Monitoring and Laboratory Tests and 8 ADVERSE REACTIONS.

Metformin hydrochloride

Hypoxic states: Cardiovascular collapse (shock), from whatever cause, 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 metformin therapy, Auro-Dapagliflozin / Metformin should be promptly discontinued.

Driving and Operating Machinery

The patient should be warned about driving a vehicle or operating machinery under conditions where a risk of hypoglycemia is present and when Auro-Dapagliflozin / Metformin is used in combination with insulin or an insulin secretagogue. See Endocrine and Metabolism. Patients should also be alerted to the elevated risk of adverse reactions related to reduced intravascular volume, such as postural hypotension, dizziness, or light-headedness.

Endocrine and Metabolism

Dapagliflozin

Diabetic ketoacidosis: Clinical trial and post-market cases of DKA, a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with T2DM treated with dapagliflozin and other SGLT2 inhibitors. In a number of reported cases, the presentation of the condition was atypical with only moderately increased blood glucose values below 13.9 mmol/L (250 mg/dL). Some cases of DKA have been fatal. See 8 ADVERSE REACTIONS.

Auro-Dapagliflozin / Metformin is not indicated and should not be used, in patients with type 1 diabetes. The diagnosis of T2DM should therefore be confirmed before initiating Auro-Dapagliflozin / Metformin.

DKA must be considered in the event of non-specific symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, anorexia, excessive thirst, and unusual fatigue or

sleepiness. **If DKA is suspected, regardless of blood glucose level, patients should discontinue Auro-Dapagliflozin / Metformin treatment and be assessed for DKA immediately.**

Conditions that can precipitate DKA while taking Auro-Dapagliflozin / Metformin include a very low carbohydrate diet (as the combination may further increase ketone body production), dehydration, high alcohol consumption and a low beta-cell function reserve. These patients should be monitored closely. Caution should also be taken when reducing the insulin dose in patients requiring insulin. See 4 DOSAGE AND ADMINISTRATION.

Prolonged diabetic ketoacidosis

Diabetic ketoacidosis may be prolonged in some patients. In most post-marketing adverse event reports, where dapagliflozin and metformin hydrochloride treatment was stopped at or before diagnosis, ketoacidosis lasted for 3 days or more despite Auro-Dapagliflozin / Metformin discontinuation and standard treatment of diabetic ketoacidosis.

Treatment interruption considerations

Temporarily discontinue treatment with dapagliflozin and metformin hydrochloride in T2DM patients who are hospitalized for major surgical procedures, or will undergo scheduled surgery, and in patients who are hospitalized for serious infections or acute serious medical illnesses. Withhold dapagliflozin and metformin hydrochloride treatment for at least 3 days, if possible, prior to major surgery or any other procedures associated with prolonged fasting, when, based on the drug pharmacology, most of dapagliflozin and metformin hydrochloride would be expected to be eliminated. Monitoring for DKA is recommended in these patients even if drug treatment has been interrupted or discontinued. Ensure risk factors for ketoacidosis are resolved prior to considering Auro-Dapagliflozin / Metformin treatment re-initiation. See 4.1 Dosing Considerations.

Use with medications known to cause hypoglycemia: Insulin and insulin secretagogues, such as sulfonylureas, causes hypoglycemia. Therefore, a lower dose of insulin or insulin secretagogues may be required to reduce the risk of hypoglycemia when used in combination with Auro-Dapagliflozin / Metformin. See 4 DOSAGE AND ADMINISTRATION and 8 ADVERSE REACTIONS.

Increases in low-density lipoprotein (LDL-C): Dose-related increases in LDL-C are seen with dapagliflozin treatment. See 8 ADVERSE REACTIONS. LDL-C levels should be monitored.

Metformin hydrochloride

Hypoglycemia: 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 lower agents 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 β-adrenergic blocking drugs.

Hypothyroidism: Metformin induces a reduction in thyrotropin (thyroid stimulating hormone (TSH)) levels in patients with treated or untreated hypothyroidism. See 8.5 Post-Market Adverse Reactions. Regular monitoring of TSH levels is recommended in patients with hypothyroidism. See Monitoring and Laboratory Tests.

Studies have shown that metformin reduces plasma TSH levels, often to subnormal levels, when it is administered to patients with untreated hypothyroidism or to hypothyroid patients effectively treated with Levothyroxine. The metformin induced reduction of plasma TSH levels is not observed when metformin is administered to patients with normal thyroid function. Metformin has been suggested to enhance the inhibitory modulation of thyroid hormones on TSH secretion.

Levothyroxine can reduce the hypoglycemic effect of metformin. Careful monitoring of blood glucose levels is recommended in patients with hypothyroidism treated with Levothyroxine, especially when thyroid hormone therapy is initiated, changed, or stopped. See 9.4 Drug-Drug Interactions, Levothyroxine.

Lactic acidosis: Lactic acidosis is a rare, but serious metabolic complication that can occur due to metformin accumulation during treatment with Auro-Dapagliflozin / Metformin; 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 hypoperfusion 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 mcg / 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). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, 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 hypoperfusion 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 patient’s ≥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 be avoided in patients with clinical or laboratory evidence of hepatic disease.

Patients should be cautioned against excessive alcohol intake, either acute or chronic, 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. See 2 CONTRAINDICATIONS.

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 bradyarrhythmias 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, but less than 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 hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. See 2 CONTRAINDICATIONS and Cardiovascular, Hepatic/Biliary/Pancreatic and Renal.

Physicians should instruct their patients to recognize the symptoms which could be a signal of the onset of lactic acidosis. If acidosis of any kind develops, Auro-Dapagliflozin / Metformin should be discontinued immediately.

Change in clinical status of previously controlled Type 2 diabetes patients:
A type 2 diabetic patient previously well controlled on Auro-Dapagliflozin / Metformin 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, Auro-Dapagliflozin / Metformin must be stopped immediately and appropriate corrective measures initiated.

Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold metformin and temporarily administer insulin. Auro-Dapagliflozin / Metformin may be reinstituted after the acute episode is resolved.

Vitamin B12 levels: Impairment of vitamin B_{12} absorption has been reported in some patients treated with metformin. Metformin commonly reduces vitamin B_{12} serum levels which may result in clinically significant vitamin B_{12} deficiency. The risk of low vitamin B_{12} levels increases with increasing metformin dose, treatment duration, and / or in patients with risk factors known to cause vitamin B_{12} deficiency. Therefore, periodic measurements of serum vitamin B_{12} are advisable in patients on long-term treatment with Auro-Dapagliflozin / Metformin.

In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on metformin and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels.

Long-term treatment with metformin has been associated with a decrease in serum vitamin B_{12} levels which may cause peripheral neuropathy. Serious cases of peripheral neuropathy have been reported with metformin treatment in the context of vitamin B_{12} deficiency. See 8.5 Post-Market Adverse Reactions. Monitoring of serum vitamin B_{12} levels is recommended. See Monitoring and Laboratory Tests.

Metformin therapy should be continued for as long as it is tolerated and not contraindicated and appropriate corrective treatment for vitamin B_{12} deficiency provided in line with current clinical guidelines.

Genitourinary

Dapagliflozin

Genital mycotic infections: Dapagliflozin increases the risk of genital mycotic infections, particularly in patients with a history of genital mycotic infections. See 8 ADVERSE REACTIONS.

Urinary tract infections (including urosepsis and pyelonephritis): Treatment with dapagliflozin increases the risk for urinary tract infections. See 8 ADVERSE REACTIONS. There have been post-marketing reports of serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization in patients treated with dapagliflozin. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

Necrotizing fasciitis of the perineum (Fournier's gangrene): Post-marketing cases of necrotizing fasciitis of perineum (Fournier's gangrene), a rare but serious and potentially life-threatening necrotizing infection requiring urgent surgical intervention, have been reported in female and male patients with diabetes mellitus receiving SGLT2 inhibitors, including dapagliflozin. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with Auro-Dapagliflozin / Metformin who present with pain or tenderness, erythema, or swelling in the genital or perineal area, with or without fever or malaise, should be evaluated for necrotizing fasciitis. If suspected, Auro-Dapagliflozin / Metformin should be discontinued and prompt treatment should be instituted (including broad-spectrum antibiotics and surgical debridement if necessary).

Hematologic

Dapagliflozin

Elevated hemoglobin and hematocrit: Mean hemoglobin and hematocrit increased in patients administered dapagliflozin, as did the number of patients with abnormally elevated values for hemoglobin / hematocrit. See 8 ADVERSE REACTIONS.

Auro-Dapagliflozin / Metformin should be used with caution in patients with an elevated hematocrit.

Metformin hydrochloride

Serious cases of metformin-induced hemolytic anemia, some with a fatal outcome, have been reported. See 8.5 Post-Market Adverse Reactions. Two mechanisms were described for the metformin-induced immune hemolytic anemia: formation of an antibody against the erythrocyte- metformin complex and autoantibody formation. Monitoring of hematologic parameters is recommended. See Monitoring and Laboratory Tests.

Hepatic / Biliary / Pancreatic

Auro-Dapagliflozin / Metformin is contraindicated in patients with severe hepatic impairment and should be avoided in patients with clinical or laboratory evidence of hepatic disease. See 2

CONTRAINDICATIONS.

Dapagliflozin
Elevations in hepatic transaminases have been reported in dapagliflozin treated patients in clinical trials; however a causal relationship with dapagliflozin has not been established. Dapagliflozin exposure is increased in patients with severe hepatic impairment. See 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY.

Metformin hydrochloride
Metformin is contraindicated in patients with clinical or laboratory evidence of hepatic disease. See 2 CONTRAINDICATIONS. Impaired hepatic function has been associated with some cases of lactic acidosis.

Serious cases of pancreatitis have been reported in patients receiving metformin. See 8.5 Post-Market Adverse Reactions. The reported pancreatitis cases occurred either in the context of an acute metformin overdose (see 5 OVERDOSAGE) or in patients receiving therapeutic doses of metformin with concurrent renal failure and / or lactic acidosis, indicating metformin accumulation.

Monitoring and Laboratory Tests

Blood glucose and HbA1c: Response to Auro-Dapagliflozin / Metformin treatment should be monitored by periodic measurements of fasting blood glucose and HbA1c levels, with a goal of decreasing these levels toward the normal range.

Due to its mechanism of action, patients taking dapagliflozin will test positive for glucose in their urine. See 9.7 Drug-Laboratory Test Interactions.

More frequent glucose monitoring should be considered when Auro-Dapagliflozin / Metformin is simultaneously administered with cationic drugs that are excreted via renal tubular secretion, or with drugs that produce hyperglycemia or hypoglycemia, especially at the initiation of treatment with the interfering drug (s) and upon their discontinuation. See 9.4 Drug-Drug Interactions, Cationic Drugs.

Hematology: Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin / hematocrit and red blood cell indices) should be performed regularly. While megaloblastic anemia has rarely been seen with metformin therapy, if this is suspected, vitamin B_{12} deficiency should be excluded.

Impairment of vitamin B_{12} absorption has been reported in some patients, and long-term treatment with metformin has been associated with reductions in vitamin B_{12} serum levels. Periodic measurements of serum Vitamin B_{12} levels should be performed in patients on long-term treatment with metformin, especially in patients with anemia or neuropathy. See Endocrine and Metabolism, Vitamin B_{12} levels.

Regular monitoring of thyroid-stimulating hormone (TSH) levels is recommended in patients with hypothyroidism. See Endocrine and Metabolism, Hypothyroidism.

Renal function: Auro-Dapagliflozin / Metformin is contraindicated in patients with severe renal impairment. See 2 CONTRAINDICATIONS and 4 DOSAGE AND ADMINISTRATION. Renal function should be assessed prior to initiation of Auro-Dapagliflozin / Metformin and regularly thereafter, with more frequent monitoring in patients whose eGFR decreases to less than 60 mL / min / 1.73 m^2.

Monitoring of renal function is required prior to, and following initiation of any concomitant drug which might have an impact on renal function.

Reduced intravascular volume: Auro-Dapagliflozin / Metformin is not recommended for use in patients who are volume depleted. Before initiating Auro-Dapagliflozin / Metformin, assess volume status, particularly in patients at risk as well as in case of intercurrent conditions that may lead to fluid loss (such as a gastrointestinal illness) for patients already taking Auro-Dapagliflozin / Metformin. In these patients, careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests, including hematocrit, serum electrolytes and renal function tests) is recommended. If volume depletion develops, temporary interruption of treatment with Auro-Dapagliflozin / Metformin should be considered until fluid loss is corrected.

LDL-cholesterol: LDL-C levels should be measured at baseline and at regular intervals during treatment with Auro-Dapagliflozin / Metformin due to dose-dependent increases in LDL-C seen with dapagliflozin therapy.

Neurologic

Metformin hydrochloride

Serious cases of metformin induced encephalopathy have been reported. See 8.5 Post-Market Adverse Reactions. Some of these cases were reported without association with lactic acidosis, hypoglycemia, or renal impairment.

Peri-Operative Considerations

Auro-Dapagliflozin / Metformin therapy should be temporarily suspended in patients who are hospitalized for any major surgical procedures or will undergo scheduled surgery (except minor procedures not associated with restricted intake of food and fluids). Auro-Dapagliflozin / Metformin should be discontinued 3 days before surgical intervention, if possible and should not be restarted until risk factors for ketoacidosis are resolved, the patient is clinically stable, the patient's oral intake has resumed and renal function has been evaluated as normal. Monitoring for DKA is recommended in these patients. See Endocrine and Metabolism and 4.1

Dosing Considerations.

Renal

Auro-Dapagliflozin / Metformin is contraindicated in patients with severe renal impairment (eGFR) <30 mL / min / 1.73 m^2). See 2 CONTRAINDICATIONS.

Dapagliflozin

The glucose-lowering benefit of dapagliflozin decreases with declining renal function. Dapagliflozin may be insufficient to improve glycemic control in patients with T2DM with an eGFR persistently <45 mL / min / 1.73 m^2. Renal function should be assessed prior to initiation of dapagliflozin and regularly thereafter. In patients with eGFR <60 mL / min / 1.73 m^2, more frequent monitoring for glycemic and renal biomarkers and signs and symptoms of renal dysfunction is recommended.

Impairment of renal function: Initiation of dapagliflozin may transiently increase serum creatinine and decreases eGFR in a dose dependent fashion. In clinical trials, renal function abnormalities have occurred after initiating dapagliflozin and metformin hydrochloride.

Post-marketing cases of acute kidney injury, including acute renal failure, shortly after the initiation of dapagliflozin and metformin hydrochloride treatment have been reported in T2DM patients. Patients with hypovolemia may be more susceptible to these changes. See 8 ADVERSE REACTIONS.

Before initiating Auro-Dapagliflozin / Metformin, consider factors that may predispose patients to acute kidney injury including hypovolemia and concomitant medications (diuretics, NSAIDs). Consider temporarily discontinuing Auro-Dapagliflozin / Metformin in any 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 Auro-Dapagliflozin / Metformin promptly and institute treatment.

Metformin hydrochloride

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. Before initiation of Auro-Dapagliflozin / Metformin therapy and while on Auro-Dapagliflozin / Metformin therapy, renal function should be assessed and verified as being within the appropriate range. In geriatric patients, Auro-Dapagliflozin / Metformin should be carefully titrated to establish the minimum dose for adequate glycemic effect. See 4.2 Recommended Dose and Dosage Adjustment, Geriatrics.
Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting

therapy with an NSAID.

Use of concomitant medications that may affect 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. See 9 DRUG INTERACTIONS.

Radiologic studies involving the use of intravascular iodinated contrast materials: Intravascular contrast studies with iodinated materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials) can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. See 2 CONTRAINDICATIONS. Therefore, in patients in whom any such study is planned, Auro-Dapagliflozin / Metformin should be temporarily discontinued at the time of or prior to the procedure, withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

7.1 Special Populations

7.1.1 Pregnant Women

Auro-Dapagliflozin / Metformin is contraindicated in pregnancy. See 2 CONTRAINDICATIONS. There are no adequate and well-controlled studies in pregnant women with dapagliflozin and metformin hydrochloride or their individual components; therefore, the safety of dapagliflozin and metformin hydrochloride in pregnant women is not known. When pregnancy is detected, Auro-Dapagliflozin / Metformin should be discontinued.

Dapagliflozin

In the time period corresponding to second and third trimesters 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 16 NON-CLINICAL TOXICOLOGY.

Metformin hydrochloride

Safety of metformin hydrochloride in pregnant women has not been established. There are no adequate and well-controlled studies of metformin in pregnant women. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg / kg / day, or about two times the maximum recommended human daily dose on a body surface area basis. Determination of fetal concentrations demonstrated a partial placental barrier to metformin. Because animal reproduction studies are not always predictive of human response, metformin is contraindicated during pregnancy. See 2 CONTRAINDICATIONS.

7.1.2 Breast-feeding

Auro-Dapagliflozin / Metformin is contraindicated in breast-feeding women. See 2 CONTRAINDICATIONS. No studies in lactating animals have been conducted with dapagliflozin and metformin hydrochloride.

Dapagliflozin

Studies in rats have shown excretion of dapagliflozin in milk. 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 16 NON-CLINICAL TOXICOLOGY.

Metformin hydrochloride
Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in patients. Metformin hydrochloride is also excreted in human breast milk in very small amounts.

7.1.3 Pediatrics

Pediatrics (<18 years of age): Safety and effectiveness of dapagliflozin and metformin hydrochloride in pediatric patients have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): Metformin is eliminated by the kidney, Auro-Dapagliflozin / Metformin should be used with caution as age increases because elderly patients are more likely to have decreased renal function. See Renal.

Dapagliflozin

A total of 2403 (26%) of the 9339 treated patients were 65 years and over and 327 (3.5%) patients were 75 years and over in the pool of 21 double-blind, controlled clinical safety and efficacy studies of dapagliflozin in patients with T2DM for improving glycemic control. After controlling for renal function (eGFR), there was no conclusive evidence suggesting that age is an independent factor affecting efficacy. No dosage adjustment is required in patients ≥65 years of age. However, in patients ≥65 years of age, a higher proportion of patients treated with

dapagliflozin had adverse events related to volume depletion and renal impairment or failure compared with placebo. The most commonly reported adverse events related to renal impairment or failure in patients ≥65 years of age in any treatment group were creatinine renal clearance decreased, renal impairment, and increased blood creatinine.

Older patients are more likely to have impaired renal function. See 8 ADVERSE REACTIONS.

In both DAPA-HF and DAPA-CKD studies the safety was similar for patients aged 65 years and younger and those older than 65. In the DAPA-HF study, 2714 (57%) out of 4744 patients with HFrEF were older than 65 years. In the DAPA-CKD study, 1818 (42%) out of 4304 patients with CKD were older than 65 years.

Metformin hydrochloride

Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients. Metformin is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, Auro-Dapagliflozin / Metformin is contraindicated in patients with severe renal impairment. See 2 CONTRAINDICATIONS. Because aging is associated with reduced renal function, Auro-Dapagliflozin / Metformin should be used with caution as age increases with careful and regular monitoring of renal function, as elderly patients are more susceptible to developing lactic acidosis. See Endocrine and Metabolism, Lactic Acidosis and Monitoring and Laboratory Tests. Auro-Dapagliflozin / Metformin treatment should not be initiated in patients older than 80 years of age, unless their renal function is not significantly reduced (see 1.2 Geriatrics). Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Auro-Dapagliflozin / Metformin should be carefully titrated to establish the minimum dose for adequate glycemic effect and generally, elderly patients should not be titrated to the maximum dose. See 4.2 Recommended Dose and Dosage Adjustment, Geriatrics.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

There have been no clinical studies conducted with dapagliflozin and metformin hydrochloride tablets. Dapagliflozin and metformin hydrochloride tablets demonstrated comparable bioavailability of dapagliflozin and metformin with co-administered tablets of dapagliflozin and metformin in a four-way crossover comparative bioavailability study. See 10.3 Pharmacokinetics.

Dapagliflozin

Clinical trials of dapagliflozin and metformin hydrochloride to improve glycemic control

The overall incidence of adverse events in a pool of patients from 8-study, short-term, placebo-controlled studies of dapagliflozin co-administered with metformin was 70% in patients treated with dapagliflozin 5 mg and metformin, 60.3% in patients treated with dapagliflozin 10 mg and metformin compared to 58.2% in patients treated with placebo+metformin.

The most commonly reported adverse events during treatment with dapagliflozin 5 mg and metformin (≥5%) were female genital mycotic infections (9.4%), nasopharyngitis (6.3%), urinary tract infections (6.1%), diarrhea (5.9%) and headache (5.4%). The most commonly reported adverse events during treatment with dapagliflozin 10 mg and metformin (≥5%) were female genital mycotic infections (9.3%), urinary tract infections (5.5%) and nasopharyngitis (5.2%).

Discontinuation of therapy due to adverse events in patients who received dapagliflozin 5 mg and metformin and dapagliflozin 10 mg and metformin was 2.0% and 4.0%, respectively compared to 3.3% for the placebo and metformin group. The most commonly reported events leading to discontinuation, and reported in more than one subject treated with dapagliflozin 5mg and metformin, were pulmonary tuberculosis and pruritus, which each were reported in 2 subjects (0.5%). The most commonly reported adverse events leading to discontinuation (experienced in at least 2 subjects) in the dapagliflozin 10 mg and metformin treatment group were decrease in creatinine renal clearance (0.2%), increased blood creatinine (0.2%), renal impairment (0.7%) and urinary tract infections (0.2%).

Dapagliflozin cardiovascular outcomes trial (DECLARE-TIMI 58)

The overall incidence of serious adverse events (SAE) in DECLARE-TIMI 58 was 34.1% in the dapagliflozin group and 36.2% in the placebo group. The most commonly reported SAEs were angina unstable (2.8% dapagliflozin vs 2.8% placebo), acute myocardial infarction (2.7% vs 2.3%), and pneumonia (1.9% vs 2.1%). Discontinuations of study drug due to an AE were reported in 8.1% and 6.9% of patients in the dapagliflozin and placebo groups, respectively. The most common events leading to discontinuation were urinary tract infection (0.5% vs 0.3%), balanoposthitis (0.3% vs <0.1%), and pollakiuria (0.2% vs 0.2%).

Metformin hydrochloride

Lactic acidosis: very rare (<1 / 10, 000 and isolated reports). See Endocrine and Metabolism, Lactic Acidosis and 5 OVERDOSAGE).

Gastrointestinal Reactions: very common (>1 / 10): gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia) are the most common reactions to metformin and are approximately 30% more frequent in patients on metformin monotherapy than in placebo-treated patients, particularly during initiation of metformin therapy. These symptoms are generally transient and resolve spontaneously during continued treatment.

Because significant diarrhea and / or vomiting can cause dehydration and prerenal azotemia,

metformin should be temporarily discontinued, under such circumstances.

For patients who have been stabilized on metformin, nonspecific gastrointestinal symptoms should not be attributed to therapy unless intercurrent illness or lactic acidosis have been excluded.

Special Senses: common (≥1 / 100): taste disturbance, i.e. metallic taste.

Dermatologic Reactions: very rare (<1 / 10,000 and isolated reports): reports of skin reactions such as erythema, pruritus, and urticaria are very rare.

Hematologic: During controlled clinical trials of 29 weeks duration, approximately 9% of patients on metformin monotherapy developed asymptomatic subnormal serum vitamin B_{12} levels; serum folic acid levels did not decrease significantly. See Endocrine and Metabolism. Five cases of megaloblastic anemia have been reported with metformin administration and no increased incidence of neuropathy has been observed.

From clinical trial and post-marketing data, a decrease / deficiency of vitamin B_{12} during use with metformin was common. Consideration of such etiology is recommended if a patient presents with megaloblastic anemia.

Hepatic: very rare (<1 / 10,000 and isolated reports): liver function tests abnormalities or hepatitis resolving upon metformin discontinuation has been documented.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Dapagliflozin and Metformin hydrochloride

Data from a prespecified pool of 8 short-term, placebo-controlled studies of dapagliflozin co-administered with metformin immediate- or extended-release was used to evaluate safety. These data reflect exposure of 1393 patients to dapagliflozin and metformin (410 patient treated with 5 mg dapagliflozin and metformin, 983 patients treated with 10 mg dapagliflozin and metformin) with an overall mean exposure duration of 158.7 days (159.6 days exposure to 5 mg dapagliflozin and metformin, 158.3 days exposure to 10 mg dapagliflozin and metformin). Table 2 shows common adverse reactions associated with the use of dapagliflozin and metformin.

Table 2 Adverse Events (Regardless of Investigator Assessment of Causality) Reported in ≥2%

of Patients Treated with Dapagliflozin 5 mg or 10 mg + Metformin and more frequently than Metformin + Placebo (24-week Short-Term Double-blind Treatment Period)

Body system / Organ Class Adverse Event	% of Patients Pool of 8 Placebo-Controlled Studies		
	Dapgliflozin 5 mg + Metformin N=410	Dapagliflozin 10 mg + Metformin N=983	Metformin + Placebo N=1185
Gastrointestinal disorders			
Constipation	2.9	1.9	1.6
Nausea	3.9	2.6	2.0
Diarrhea	5.9	4.2	5.6
Infections and infestations			
Influenza	4.1	2.6	2.4
Nasopharyngitis	6.3	5.2	5.9
Urinary Tract Infection[€]	6.1	5.5	3.6
Pharyngitis	2.7	1.5	1.1
Female genital mycotic infection[λ]	9.4	9.3	1.5
Male genital mycotic infection[¥]	4.3	3.6	0
Metabolism and nutrition disorders			
Dyslipidemia	2.7	1.5	1.4
Musculoskeletal and connective tissue disorders			
Back pain	3.4	2.5	3.2
Nervous system disorders			
Headache	5.4	3.3	2.8
Dizziness	3.2	1.8	2.2
Renal and urinary disorders			
Dysuria	2.2	1.6	1.1
Increased urination[±]	2.4	2.6	1.4
Respiratory, thoracic and mediastinal disorders			
Cough	3.2	1.4	1.9

[€] Urinary tract infections include the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, urethritis, prostatitis and pyelonephritis.

λ Genital mycotic infections include the following preferred terms, 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: dapagliflozin 5 mg=223, dapagliflozin 10 mg=430, Placebo=534).

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

± Increased urination includes the following preferred terms, listed in order of frequency reported: pollakiuria,

polyuria, and urine output increased.

Dapagliflozin

Three major pools of patients were used to evaluate adverse reactions with dapagliflozin 5 mg and 10 mg versus control, including two placebo-controlled study pools and a larger pool of active- and placebo-controlled studies. In addition, adverse reactions were evaluated with dapagliflozin 10 mg versus placebo in a dedicated CV outcomes trial (DECLARE-TIMI 58).

Placebo-Controlled Studies for dapagliflozin 5 mg and 10 mg: The first pool of patients was derived from 12 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.

Pool of 13 Placebo-Controlled Studies for Dapagliflozin 10 mg: The safety and tolerability of dapagliflozin 10 mg was also evaluated in a larger placebo-controlled study pool. This pool combined 13 placebo-controlled studies, including 3 monotherapy studies, 9 add-on 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.

Active- and Placebo-Controlled Studies: The third pool of patients was derived from 21 active- and placebo-controlled studies used to evaluate and present data for malignancies and liver tests. In this pool, 5936 patients were treated with dapagliflozin and 3403 were treated with control (either as monotherapy or in combination with other antidiabetic therapies).

Cardiovascular Outcomes Trial (DECLARE-TIMI 58): The safety and tolerability of dapagliflozin 10 mg, as add-on to standard of care therapy, was also evaluated in a dedicated CV outcomes study in adult patients with T2DM and CV risk factors or established cardiovascular disease. In this study, 8574 patients received dapagliflozin 10 mg and 8569 received placebo for a mean exposure time of 42 months.

The adverse events in the 12-study placebo-controlled pooled analysis reported in ≥2% of patients treated with dapagliflozin 5 mg or 10 mg, and occurring more frequently than in patients treated with placebo, are shown in Table 3.

Table 3 Adverse Events Reported in ≥2% of Patients Treated with Dapagliflozin 5 mg or 10 mg and More Frequently than in Patients Treated with Placebo

System organ class Preferred term	% of Patients (Pool of 12 Placebo-controlled Studies)		
	Dapagliflozin 5 mg N=1145	Dapagliflozin 10 mg N=1193	Placebo N=1393
Gastrointestinal disorders			
Constipation	2.2	1.9	1.5
Nausea	2.8	2.5	2.4
Infections and infestations			
Influenza	2.7	2.3	2.3
Nasopharyngitis	6.6	6.3	6.2
Female genital mycotic infection†	8.4	6.9	1.5
Male genital mycotic infection‡	2.8	2.7	0.3
Urinary Tract Infection§	5.7	4.3	3.7
Metabolism and nutrition disorders			
Dyslipidemia	2.1	2.5	1.5
Musculoskeletal and Connective Tissue Disorders			
Back pain	3.1	4.2	3.2
Pain in extremity	2.0	1.7	1.4
Renal and Urinary disorders			
Increased urination¶	2.9	3.8	1.7
Discomfort with urination	1.6	2.1	0.7

† Genital mycotic infections include the following preferred terms, 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: dapagliflozin 5 mg=581, dapagliflozin 10 mg=598, Placebo=677).

‡ Genital mycotic infections include the following preferred terms, listed in order of frequency reported for males: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection male, penile infection, balanoposthitis, balanoposthitis infective, genital infection and posthitis (N for males: dapagliflozin 5 mg=564, dapagliflozin 10 mg=595, Placebo=716).

§ Urinary tract infections include the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection, and prostatitis.

¶ Increased urination includes the following preferred terms, listed in order of frequency reported: pollakiuria, polyuria, and urine output increased.

Additional adverse events in ≥5% of patients treated with dapagliflozin seen more frequently than in patients in the placebo / comparator group, and reported in at least three or more patients treated with dapagliflozin 5 mg or 10 mg are described below by treatment regimen.

Table 4 Adverse Events Reported in ≥5% of Patients Treated with Dapagliflozin 5 mg or 10 mg and Observed More Frequently than in Patients Treated with Placebo / Comparator and Reported in at least Three or More Patients Treated with Dapagliflozin 5 mg or 10 mg

Treatment Regimen Adverse Event (Preferred term)	n (%) of Patients		
	Dapagliflozin 5 mg	Dapagliflozin 10 mg	Placebo / Comparator
Monotherapy	N=132	N=146	N=75
Diarrhea	8 (6.1)	4 (2.7)	1 (1.3)
Upper respiratory infection	2 (1.5)	9 (6.2)	1 (1.3)
Arthralgia	8 (6.1)	7 (4.8)	1 (1.3)
Headache	12 (9.1)	13 (8.9)	5 (6.7)
Add-on to Metformin	N=137	N=135	N=137
Diarrhea	5 (3.6)	10 (7.4)	7 (5.1)
Headache	10 (7.3)	11 (8.1)	6 (4.4)
Add-on to Metformin versus Glipizide	Dapagliflozin (any dose) N=406		N=408
Headache	21 (5.2)		17 (4.2)

Description of Selected Adverse Reactions[1]

Volume depletion and hypotension: Events related to volume depletion (including reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension) were reported in 0.6%, 0.8% and 0.4% of patients who received dapagliflozin 5 mg, dapagliflozin 10 mg and placebo, respectively, in the 12-study, short-term, placebo-controlled pool. Serious events occurred in ≤0.2% of patients across the 21 active- and placebo-controlled studies and were balanced between dapagliflozin 10 mg and comparator.

Postural blood pressure measurement revealed orthostatic hypotension in 13.1% of patients treated with dapagliflozin 10 mg vs. 11.3% of patients treated with placebo over the 24-week treatment period. In addition, in two studies with patients with type 2 diabetes and hypertension, postural blood pressure measurement revealed orthostatic hypotension in 3.2% of dapagliflozin 10 mg-treated patients vs. 1.7% of placebo-treated patients across the two studies over the 12- week treatment period.

Genital mycotic infections: Events of genital mycotic infections were reported in 5.7% (65 / 1145), 4.8% (57 / 1193) and 0.9% (12 / 1393) of patients who received dapagliflozin 5 mg, dapagliflozin 10 mg and placebo, respectively, in the 12-study, short-term, placebo-controlled pool. Infections were more frequently reported in females (8.4% [49 / 581], 6.9% [41 / 598] dapagliflozin 5 mg and 10 mg, respectively, vs. 1.5% [10 / 677] placebo) than in males (2.8% [16 / 564], 2.7% [16 / 595] dapagliflozin 5 mg and 10 mg, respectively vs. 0.3% [2 / 716] placebo). The most frequently

reported genital infections were vulvovaginal mycotic infections in females, and balanitis in males (see Table 3).

[1] Based on medical assessment (including biological plausibility / mechanism of action) of adverse events reported in <2% of subjects in the 12-study placebo-controlled pool.

Patients who had a previous history of recurrent genital mycotic infections, were more likely to have an event of genital infection during the study than those without a history of infection (23.1%, [3 / 13] 25.0% [3 / 12] and 10.0% [1 / 10] versus 5.9% [60 / 1013], 5.0% [53 / 1053] and 0.8% [10 / 1247] on dapagliflozin 5 mg, dapagliflozin 10 mg and placebo, respectively).

Urinary tract infections: Events of urinary tract infections (UTI) were reported in 5.7% (65 / 1145), 4.3% (51 / 1193), and 3.7% (52 / 1393) of patients who received dapagliflozin 5 mg, dapagliflozin 10 mg and placebo, respectively, in the 12-study, short-term, placebo-controlled pool. Infections were more frequently reported in females (9.6% [56 / 581] and 7.7% [46 / 598] dapagliflozin 5 mg and 10 mg, respectively, vs. 6.6% [45 / 677] placebo) than in males (1.6% [9 / 564] and 0.8% [5 / 595] dapagliflozin 5 mg and 10 mg, respectively, vs. 1.0% [7 / 716] placebo).

In 9 of the 13 studies in the dapagliflozin 10 mg placebo-controlled pool for which long-term treatment data were available (mean duration of treatment 439.5 days for dapagliflozin 10 mg and 419.0 days for placebo), of the 174 patients treated with dapagliflozin 10 mg who experienced an infection, 135 (77.6%) had only one and 11 (6.3%) had 3 or more. Of the 121 patients treated with placebo who experienced an infection, 94 (77.7%) had only one and 12 (9.9%) had 3 or more.

In the 13-study, short-term, placebo-controlled pool, patients who had a previous history of recurrent urinary tract infection, were more likely to have an event of urinary tract infection (6.0% [26 / 436] of patients with history of infection treated with dapagliflozin 10 mg and 5.9% [24 / 407] of patients with history of infection on placebo) during the study than those without a history of infection (4.4% [84 / 1924] on dapagliflozin 10 mg and 3.0% [57 / 1888] on placebo).

Hypoglycemia: The frequency of hypoglycemia depended on the type of background therapy used in each study (see Table 5). Studies of dapagliflozin as an add-on to insulin therapy had higher rates of hypoglycemia with dapagliflozin treatment than with placebo treatment. See 7 WARNINGS AND PRECAUTIONS.

Table 5 Incidence of Major* and Minor† Hypoglycemia in Placebo-Controlled Studies

	Dapagliflozin 5 mg	Dapagliflozin 10 mg	Placebo
Add-on to Metformin (24 weeks)	N=137	N=135	N=137
Major [n (%)]	0	0	0
Minor [n (%)]	2 (1.5)	1 (0.7)	0
Active Control Add-on to Metformin vs. Glipizide (52 weeks)	-	N=406	N=408
Major [n (%)]	-	0	3 (0.7)
Minor [n (%)]	-	7 (1.7)	147 (36.0)
Add-on to Metformin and Sulfonylurea (24 weeks)	-	N = 109	N = 109
Major [n (%)]	-	0	0
Minor [n (%)]	-	14 (12.8)	4 (3.7)

	Dapagliflozin 5 mg	Dapagliflozin 10 mg	Placebo
Add-on to Sitagliptin alone or with metformin (24 weeks)	-	N = 225	N = 226
Major [n (%)]	-	1 (0.4)	0
Minor [n (%)]	-	4 (1.8)	3 (1.3)
Add-on to Insulin with or without other OADs‡ (24 weeks)	N=212	N=196	N=197
Major [n (%)]	1 (0.5)	1 (0.5)	1 (0.5)
Minor [n (%)]	92 (43.4)	79 (40.3)	67 (34.0)
CV outcomes study (42 months mean exposure) §			
All Patients	-	**N=8574**	**N=8569**
Major [n (%)]	-	58 (0.7)	83 (1.0)
Minor [n (%)]	-	Not collected	Not collected
Patients treated with Insulin	-	**N=4177**	**N=4606**
Major [n (%)]	-	52 (1.2)	64 (1.4)
Patients treated with a Sulfonylurea	-	**N=4118**	**N=4521**
Major [n (%)]	-	14 (0.3)	23 (0.5)

* Major episodes of hypoglycemia were defined as symptomatic episodes requiring external (third party) assistance due to severe impairment in consciousness or behaviour with a capillary or plasma glucose value <3 mmol / L 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 <3.5 mmol / L regardless of need for external assistance or an asymptomatic capillary or plasma glucose measurement <3.5 mmol / L which did not qualify as a major episode.

‡ OAD=oral antidiabetic therapy.

§ Patients were on treatment at the time of the events.

Add-on to metformin: In studies with dapagliflozin as an add-on to metformin there were no major episodes of hypoglycemia reported. In these studies, the frequency of minor episodes of hypoglycemia was similar (<5%) across the treatment groups, including placebo.

In an add-on to metformin study that compared dapagliflozin to glipizide up to 104 weeks, there were 3 episodes (0.7%) of major hypoglycemia in patients treated with glipizide plus metformin and none in patients treated with dapagliflozin plus metformin. Minor episodes of hypoglycemia were reported in 2.5% of patients treated with dapagliflozin plus metformin and 42.4% of patients treated with glipizide plus metformin.

Add-on to metformin and to a sulfonylurea: In the add-on to combination study with metformin and a sulfonylurea up to 52 weeks, there were no episodes of major hypoglycemia reported. Minor episodes of hypoglycemia were reported for 15.6% of patients treated with dapagliflozin 10 mg plus metformin and a sulfonylurea and 4.6% of patients treated with placebo plus metformin and a sulfonylurea.

Add-on to sitagliptin alone or with metformin: In a study of dapagliflozin 10 mg added on to sitagliptin (with or without metformin) for up to 48 weeks, one major episode of hypoglycemia was reported in a patient treated with dapagliflozin 10 mg plus sitagliptin (without metformin).

Minor episodes of hypoglycemia were reported in 2.2% and 1.3% of patients treated with dapagliflozin 10 mg or placebo added on to sitagliptin (with or without metformin), respectively.

Add-on to insulin: At Week 104, major episodes of hypoglycemia were reported in 1.4%, 1.0% and 0.5% of patients treated with dapagliflozin 5 mg and 10 mg or placebo added on to insulin, respectively. Minor episodes were reported in 52.8%, 53.1% and 41.6% of patients treated with dapagliflozin 5 mg or 10 mg or placebo added on to insulin, respectively. In two additional studies that also included a large proportion of patients who received insulin as background therapy (alone or with one or more oral antidiabetic treatments) (see 14 CLINICAL TRIALS), the rate of minor episodes of hypoglycemia was also increased in patients treated with dapagliflozin 10 mg compared with those treated with placebo.

CV outcomes study (DECLARE-TIMI 58): Major events of hypoglycemia were reported in 58 patients (0.7%) treated with dapagliflozin 10 mg and 83 (1.0%) patients treated with placebo. Major events of hypoglycemia were reported in 52 patients (1.2%) and 64 patients (1.4%) treated with dapagliflozin 10 mg or placebo added on to insulin, respectively. Major events of hypoglycemia were reported in 14 patients (0.3%) and 23 patients (0.5%) treated with dapagliflozin or placebo added on to sulfonylurea, respectively. Major events of hypoglycemia leading to hospitalization occurred in 13 patients (0.2%) and 22 patients (0.3%) treated with dapagliflozin or placebo, respectively.

Patients with renal impairment: Safety was assessed in a dedicated study of diabetic patients with moderate renal impairment (eGFR ≥30 to <60 mL / min / 1.73m^2). At Week 52, dapagliflozin was associated with changes from baseline in mean eGFR (eGFR: dapagliflozin 5 mg: -2.08 mL / min / 1.73m^2, dapagliflozin 10 mg -4.46 mL / min / 1.73m^2 and placebo -2.58 mL / min / 1.73m^2). At Week 104, these changes persisted (eGFR: dapagliflozin 5 mg –1.71 mL / min / 1.73m^2, dapagliflozin 10 mg -3.50 mL / min / 1.73m^2 and placebo -2.38 mL / min / 1.73m^2). With dapagliflozin 5 mg and 10 mg, these eGFR reductions were evident at Week 1 while placebo treated patients had a slow continuous decline through Week 104.

Diabetic ketoacidosis: Cases of DKA, a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with type 2 diabetes treated with dapagliflozin and other SGLT2 inhibitors. Some cases of DKA have been fatal. Auro-Dapagliflozin / Metformin is not indicated, and should not be used, in patients with type 1 diabetes. In some cases, the presentation of the condition was atypical, with blood glucose values only moderately elevated (<13.9 mmol / L (250 mg / dL)). See Endocrine and Metabolism.

Cardiovascular Outcomes Study (DECLARE-TIMI 58)

DECLARE-TIMI 58 evaluated the safety and tolerability of dapagliflozin 10 mg (n=8574) versus placebo (n=8569) in adult patients with T2DM and CV risk factors or established cardiovascular disease. The mean exposure time was 42 months. In total, there were 30623 patient-years of exposure to dapagliflozin. The safety variables collected in DECLARE-TIMI 58 included: serious adverse events (SAE), adverse events leading to discontinuation of study drug (DAE), CV events,

amputation events, DKA events, and adverse events of special interest. Adverse events of special interest consisted of: malignancies, hepatic events, major hypoglycemic events, fractures, renal events, symptoms of volume depletion, hypersensitivity reactions, urinary tract infections, and genital infections.

Events related to volume depletion were reported in 2.5% and 2.4% of patients in the dapagliflozin and placebo groups, respectively. Serious adverse events (SAE) of volume depletion were reported in 0.9% and 0.8% of patients in the dapagliflozin and placebo groups, respectively. In patients with eGFR <60mL / min / 1.73m^2 at baseline, SAEs were reported in 3.1% and 2.0% of patients in the dapagliflozin and placebo groups, respectively. In patients ≥65 years, SAEs were reported in 1.3% and 1.1% of patients in the dapagliflozin and placebo groups, respectively.

Events of genital infection leading to discontinuation of study drug occurred in 0.9% and <0.1% of patients in the dapagliflozin and placebo groups, respectively. SAEs of genital infection occurred in 2 patients (<0.1%) in each of the dapagliflozin and placebo groups.

Events of UTI leading to discontinuation of study drug occurred in 0.7% and 0.4% of patients in the dapagliflozin and placebo groups, respectively. SAEs of UTI occurred 0.9% and 1.3% of patients in the dapagliflozin and placebo groups, respectively. In patients ≥75 years of age, events of UTI leading to discontinuation of study drug occurred in 1.7% and 0.4% of patients in the dapagliflozin and placebo groups, respectively; SAEs of UTI occurred in 2.0% and 1.4% of patients in the dapagliflozin and placebo groups, respectively.

Adjudicated events of DKA were reported in 27 patients (0.3%) in the dapagliflozin 10 mg group and 12 patients (0.1%) in the placebo groups (0.04 and 0.09 events per 100 patient-years, respectively). The events were evenly distributed throughout 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.

Renal events (e.g., decreased renal creatinine clearance, renal impairment, increased blood creatinine, and decreased glomerular filtration rate) were reported in 4.9% and 6.1% of patients in the dapagliflozin and placebo groups, respectively.

Events of acute kidney injury were reported in 1.5% and 2.0% of patients in the dapagliflozin and placebo groups, respectively. SAEs of renal events occurred in 0.9% and 1.6% of patients in the dapagliflozin and placebo groups, respectively.

Events of fractures occurred in 7.4% and 5.8% of patients ≥75 years of age in the dapagliflozin and placebo groups, respectively.

8.3 Less Common Clinical Trial Adverse Reactions

Gastrointestinal disorder: dry mouth

Investigations: weight decreased
Metabolism and nutrition disorders: dehydration, hypotension, thirst
Renal and urinary disorders: glomerular filtration rate decreased, nocturia
Reproductive and breast disorders: pruritus genital, vulvovaginal pruritus

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Dapagliflozin

Increases in serum creatinine, blood urea nitrogen (BUN) and decreased eGFR: In the pool of 13 placebo-controlled studies, in dapagliflozin-treated patients, mean eGFR decreased by Week 1 and then increased toward eGFR baseline values over time to Week 24. Changes from baseline in serum creatinine were consistent with changes in eGFR. Mean serum creatinine levels increased at Week 1 and decreased toward baseline at Week 24. There were small increases in BUN. Mean BUN levels increased at Week 1 and values remained stable through Weeks 24 and 102.

Table 6 Mean Changes from Baseline for Serum Creatinine and eGFR at Week 1 and Week 24

Study Week / Treatment Group	Week 1*		Week 24*	
	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo
Serum creatinine, µmol / L (mg / dL)				
Mean Changes from Baseline	-3.62 (-0.041) N=1112	-0.71 (-0.008) N=1057	1.68 (0.019) N=1954	0.71 (0.008) N=1844
eGFR, mL / min / 1.73m^2				
Mean Changes from Baseline	-4.174 N=1102	0.490 N=1048	-1.446 N=1954	-0.665 N=1844

*Pool of 13 placebo-controlled studies

Increases in hemoglobin / hematocrit: In the pool of 13 placebo-controlled studies, increases from baseline in mean hemoglobin values were observed and 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. The mean changes from baseline in hemoglobin and hematocrit at Weeks 24 and 102 are presented below.

Table 7 Mean Changes from Baseline for Hematocrit at Week 24 and Week 102

Study Week / Treatment Group	Week 24*		Week 102**	
	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo
Hemoglobin, g / L (g / dL)				
Mean Changes from Baseline	6.21 (0.621) N=1934	-1.38 (-0.138) N=1828	7.0 (0.70) N=621	-2.1 (-0.21) N=515
Hematocrit, %				
Mean Changes from Baseline	2.30 N=1908	-0.33 N=1796	2.68 N=616	-0.46 N=510

*Pool of 13 placebo-controlled studies
**Pool of 9 placebo-controlled studies

By Week 24, hematocrit values >55% were reported in 1.3% of dapagliflozin 10 mg-treated patients vs. 0.4% of placebo-treated patients. Results were similar during the short-term plus long-term phase (the majority of patients were exposed to treatment for more than one year).

Increases in serum inorganic phosphorus: In the pool of 13 placebo-controlled studies, increases from baseline in mean serum phosphorus levels were reported at Week 24 in dapagliflozin 10 mg-treated patients compared with placebo-treated patients. Similar results were seen at Week 102 (see below). Higher proportions of patients with marked laboratory abnormalities of hyperphosphatemia were reported in dapagliflozin 10 mg group vs. placebo at Week 24 and during the short-term plus long-term phase. The clinical relevance of these findings is unknown.

Table 8 Mean Changes from Baseline for Serum Inorganic Phosphorus and Proportion of Patients with Hyperphosphatemia at Week 24 and Week 102

Study Week / Treatment Group	Week 24*		Week 102**	
	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo
Serum Inorganic Phosphorus, µmol / L (mg / dL)				
Mean Changes from Baseline	42.0 (0.13) N=1954	-12.9 (-0.04) N=1844	38.7 (0.12) N=627	6.5 (0.02) N=522
Hyperphosphatemia†				
Proportion of Patients	1.7% N=1178	0.7% N=1381	3.0% N=2001	1.6% N=1940

*Pool of 13 placebo-controlled studies
**Pool of 9 placebo-controlled studies
†Defined as ≥1.81 mmol/L (≥5.6 mg/dL) if age 17 - 65 or ≥1.65 mmol/L (≥5.1 mg/dL) if ≥age 66

Lipids: In the pool of 13 placebo-controlled studies, increases from baseline were noted in levels of total cholesterol, LDL- and HDL-cholesterol, and decreases from baseline were noted for triglycerides at Week 24 and Week 102 in dapagliflozin 10 mg-treated patients compared with placebo-treated patients (see below).

Table 9 Mean Changes from Baseline for Lipid Parameters at Week 24 and Week 102

Study Week / Treatment Group	Week 24*		Week 102**	
	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo
Mean Percent Changes from Baseline				
Total Cholesterol	2.5% N=1851	0.0% N=1747	2.1% N=550	-1.5% N=446
HDL-cholesterol	6.0% N=1851	2.7% N=1748	6.6% N=549	2.1% N=447
LDL-cholesterol	2.9% N=1840	-1.0% N=1736	2.9% N=542	-2.2% N=442
Triglycerides	-2.7% N=1844	-0.7% N=1736	-1.8% N=545	-1.8% N=444

*Pool of 13 placebo-controlled studies
**Pool of 9 placebo-controlled studies

The ratio between LDL-cholesterol and HDL-cholesterol decreased for both treatment groups at Week 24 and at Week 102.

Metformin hydrochloride

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. See 7 WARNINGS AND PRECAUTIONS.

8.5 Post-Market Adverse Reactions

Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Metformin hydrochloride

Blood and Lymphatic System Disorders: hemolytic anemia, some with a fatal outcome.

Gastrointestinal disorders: abdominal discomfort, abdominal distension, abdominal pain, abdominal pain upper, constipation, diarrhea, dry mouth, dyspepsia, flatulence, gastric disorder, gastric ulcer, gastrointestinal disorder, nausea, vomiting

Hepatobiliary disorders: liver function tests abnormalities or hepatitis resolving upon metformin discontinuation, autoimmune hepatitis, drug-induced liver injury, hepatitis, pancreatitis

Investigations: blood lactic acid increased. Reduction of thyrotropin level in patients with treated or untreated hypothyroidism.

Metabolism and nutrition disorders: lactic acidosis, decrease of vitamin B_{12} absorption with decrease of serum levels during long-term use of metformin, weight decreased, decreased appetite. Hypomagnesemia in the context of diarrhea.

Nervous System Disorders: encephalopathy, peripheral neuropathy in patients with vitamin B_{12} deficiency

Skin and subcutaneous tissue disorders: photosensitivity, erythema, pruritus, rash, skin lesion, urticaria

Dapagliflozin

Genitourinary: severe urinary tract infections; urosepsis and pyelonephritis

Hepatic / Biliary / Pancreatic: acute pancreatitis

Infection and Infestations: necrotizing fasciitis of the perineum (Fournier's gangrene). See Genitourinary.

Metabolism and nutrition disorders: diabetic ketoacidosis

Renal and urinary disorders: acute kidney injury, including acute renal failure

Skin and subcutaneous tissue disorders: rash (including rash generalized, rash pruritic, rash macular, rash macula-papular, rash pustular, rash vesicular)

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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

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. 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.

Metformin hydrochloride

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

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

9.3 Drug-Behavioural Interactions

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

Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking Auro-Dapagliflozin / Metformin, since alcohol intake potentiates the effect of metformin on lactate metabolism. The risk of lactic acidosis is increased in acute alcohol intoxication, particularly in case of fasting or malnutrition or hepatic insufficiency. Auro-Dapagliflozin / Metformin is contraindicated in patients with clinical or laboratory evidence of hepatic disease. It is recommended that consumption of alcohol and alcohol-containing medicinal product be avoided. See 2 CONTRAINDICATIONS.

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be alerted to the elevated risk of adverse reactions related to reduced intravascular volume, such as postural dizziness, and to the risk of hypoglycemia when Auro-Dapagliflozin / Metformin is used as add-on therapy with insulin or an insulin secretagogue.

9.4 Drug-Drug Interactions

Dapagliflozin

Effect of other drugs on dapagliflozin

In studies conducted in healthy subjects, the pharmacokinetics of dapagliflozin was not altered by the co-administered drugs (see Table 10).

Table 10 Effects of Co-administered Drugs on Dapagliflozin Systemic Exposure

Co-administered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Effect on Dapagliflozin Exposure Ratio of Adjusted Geometric Means (90% CI)		Clinical Comment
		Cmax	AUC†	
Oral Antidiabetic Agents				
Metformin (1000 mg)	20 mg	0.932 (0.848, 1.024)	0.995 (0.945, 1.053)	No dosing adjustment required
Pioglitazone (45 mg)	50 mg	1.09 (1.00, 1.18)	1.03 (0.98, 1.08)	No dosing adjustment required
Sitagliptin (100 mg)	20 mg	0.958 (0.875, 1.049)	1.081 (1.031, 1.133)	No dosing adjustment required
Glimepiride (4 mg)	20 mg	1.006 (0.921, 1.097)	0.989 (0.958, 1.020)	No dosing adjustment required
Voglibose (0.2 mg three times daily)	10 mg	1.040 (0.899, 1.204)	1.009 (0.954, 1.067)	No dosing adjustment required
Other Medications				
Hydrochlorothiazide (25 mg)	50 mg	NC	1.07 (1.04, 1.11)	No dosing adjustment required
Bumetanide (1 mg)	10 mg once daily for 7 – 14 days	1.080 (0.953, 1.222)	1.047 (0.991, 1.106)	No dosing adjustment required
Valsartan (320 mg)	20 mg	0.881 (0.796, 0.975)	1.024 (1.000, 1.049)	No dosing adjustment required
Simvastatin (40 mg)	20 mg	0.978 (0.887, 1.078)	0.986 (0.957, 1.017)	No dosing adjustment required
Mefenamic acid (250 mg every 6 hours)	10 mg	1.13 (1.03, 1.24)	1.51 (1.44, 1.58)	No dosing adjustment required
Anti-infective Agent				
Rifampin (600 mg once daily for 6 days)**	10 mg	0.931 (0.779, 1.112)	0.780 (0.731, 0.832)	No dosing adjustment required

* Single dose unless otherwise noted.

NC No apparent change, ratio and 90% CI were not calculated.

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

** The mean amount of glucose excreted in the urine over 24 h following administration of dapagliflozin alone (51 g) was not markedly affected by rifampin co-administration (45 g).

Effect of dapagliflozin on other drugs

In studies conducted in healthy subjects, as described below, dapagliflozin did not alter the pharmacokinetics of the co-administered drugs (see Table 11).

Table 11 Effects of Dapagliflozin on the Systemic Exposures of Co-administered Drugs

Co-administered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Effect on Co-administered Drug Exposure Ratio of Adjusted Geometric Means (90% CI)		Clinical Comment
		C_{max}	AUC†	
Oral Antidiabetic Agents				
Metformin (1000 mg)	20 mg	0.953 (0.866, 1.049)	1.001 (0.933, 1.075)	No dosing adjustment required
Pioglitazone (45 mg)	50 mg	0.93 (0.75, 1.15)	1.00 (0.90, 1.13)	No dosing adjustment required
Sitagliptin (100 mg)	20 mg	0.887 (0.807, 0.974)	1.012 (0.985, 1.040)	No dosing adjustment required
Glimepiride (4 mg)	20 mg	1.043 (0.905, 1.201)	1.132 (0.996, 1.287)	No dosing adjustment required
Other Medications				
Hydrochlorothiazide (25 mg)	50 mg	NC	0.99 (0.95, 1.04)	No dosing adjustment required
Bumetanide (1 mg)**	10 mg once daily for 7 days	1.132 (0.979, 1.310)	1.132 (0.985, 1.302)	No dosing adjustment required
Valsartan (320 mg)	20 mg	0.938 (0.762, 1.156)	1.046 (0.850, 1.286)	No dosing adjustment required
Simvastatin (40 mg)	20 mg	0.936 (0.816, 1.073)	1.193 (1.018, 1.399)	No dosing adjustment required
Oral Antidiabetic Agents				
Digoxin (0.25 mg)	20 mg loading dose then 10 mg once daily for 7 days	0.990 (0.843, 1.162)	1.002 (0.860, 1.167)	No dosing adjustment required

Co-administered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Effect on Co-administered Drug Exposure Ratio of Adjusted Geometric Means (90% CI)		Clinical Comment
		C_{max}	AUC†	
Warfarin (25 mg)***	20 mg loading dose then 10 mg once daily for 7 days	S-warfarin 1.030 (0.994, 1.124)	1.068 (1.002, 1.138)	No dosing adjustment required
		R-warfarin 1.057 (0.977, 1.145)	1.079 (1.030, 1.130)	

* Single dose unless otherwise noted.

NC No apparent change, ratio and 90% CI were not calculated.

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

** Co-administration of dapagliflozin did not meaningfully alter the steady-state pharmacodynamic responses (urinary sodium excretion, urine volume) to bumetanide in healthy subjects.

*** Dapagliflozin also did not affect the anticoagulant activity of warfarin as measured by the prothrombin time (International Normalized Ratio; [INR]).

Diuretics: Dapagliflozin may add to the diuretic effect of loop diuretics and may increase the risk of dehydration and hypotension. See 7 WARNINGS AND PRECAUTIONS.

Lithium: Concomitant use of Auro-Dapagliflozin / Metformin, or other SGLT2 inhibitors, with lithium may lead to a reduction in serum lithium concentrations due to a possible increased urinary clearance of lithium. Therefore, serum lithium concentration should be monitored more frequently with Auro-Dapagliflozin / Metformin initiation or following dose changes. Patients should be referred to their lithium prescribing healthcare professional to monitor serum concentration of lithium.

Metformin hydrochloride

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 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 co-administered 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. Tmax and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

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 an interaction has been observed between metformin and oral cimetidine 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. Therefore, careful patient monitoring and dose adjustment of metformin or the interfering drug is recommended in patients who are taking cationic medications that are excreted via renal tubular secretion.

Anticoagulant: Elimination rate of the anticoagulant phenprocoumon has been reported to be increased by 20% when used concurrently with metformin. Therefore, patients receiving phenprocoumon or other antivitamin K anticoagulants should be monitored carefully when both types of drugs are used simultaneously. In such cases, an important increase of prothrombin time may occur upon cessation of Auro-Dapagliflozin / Metformin therapy, with an increased risk of hemorrhage.

Levothyroxine: Levothyroxine can reduce the hypoglycemic effect of metformin. Monitoring of blood glucose levels is recommended, especially when thyroid hormone therapy is initiated, changed, or stopped. See Monitoring and Laboratory Tests. Auro-Dapagliflozin / Metformin dosage should be adjusted as necessary. See 4.1 Dosing Considerations, Levothyroxine.

Other: Other drugs tend to produce hyperglycemia and may lead to loss of blood sugar control. These include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, estrogen plus progestogen, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, isoniazid and beta-2-agonists. ACE inhibitors may decrease the blood glucose levels. When such drugs are administered to a patient receiving metformin the patient should be closely observed to maintain adequate glycemic control.

Diuretics, especially loop diuretics, may increase the risk of lactic acidosis due to their potential to decrease renal function.

9.5 Drug-Food Interactions

Interactions with food have not been studied.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Dapagliflozin

Due to its mechanism of action, patients taking dapagliflozin will test positive for glucose in their urine.

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.

Metformin hydrochloride

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. See 2 CONTRAINDICATIONS and Renal.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Dapagliflozin and metformin hydrochloride

Auro-Dapagliflozin / Metformin combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with T2DM: dapagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Dapagliflozin

Dapagliflozin is a reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2) that improves glycemic control in patients with T2DM by reducing renal glucose reabsorption leading to urinary excretion of excess glucose (glycuresis).

SGLT2 is selectively expressed in the kidney. SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Dapagliflozin

improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary excretion of excess glucose. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycemia. Dapagliflozin acts independently of insulin secretion and insulin action.

Urinary glucose excretion (glucuresis) induced by dapagliflozin is associated with caloric loss and reduction in weight. 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 vs. SGLT1, the major transporter in the gut responsible for glucose absorption.

The Ki (inhibition constant) value for human SGLT2 is 0.2nM with selectivity vs. human SGLT1 of >3000-fold. Dapagliflozin is also highly selective for SGLT2 vs. the facilitative glucose transporters GLUT1, GLUT2 and GLUT4. The major human metabolite of dapagliflozin, dapagliflozin 3-O-glucuronide, is 2500-fold less active at SGLT2 and is not expected to have pharmacologic activity at clinical relevant doses. Oral administration of dapagliflozin to normal and diabetic animal models increases the excretion of glucose in the urine and increases urine volume. In diabetic animal models, dapagliflozin lowers plasma glucose and demonstrates positive effects on insulin sensitivity and preservation of beta-cell function.

Metformin hydrochloride

Metformin is a biguanide derivative producing an antihyperglycemic effect which can only be observed in man or in the diabetic animal and only when there is insulin secretion. Metformin, at therapeutic doses, does not cause hypoglycemia when used alone in man or in the non-diabetic animal, except when using a near lethal dose. Metformin has no effects on the pancreatic beta cells. The mode of action of metformin is not fully understood. It has been postulated that metformin might potentiate the effect of insulin or that it might enhance the effect of insulin on the peripheral receptor site. This increased sensitivity seems to follow an increase in the number of insulin receptors on cell surface membranes.

10.2 Pharmacodynamics

Dapagliflozin

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients with T2DM following the administration of dapagliflozin. 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 T2DM 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 T2DM 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 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 18.3 to 48.3 µmol / L (0.33 mg / dL to 0.87 mg / dL).

Cardiac electrophysiology: In a double-blind, randomized, placebo- and positive-controlled crossover study, single oral doses of dapagliflozin 20 mg and 150 mg were not associated with clinically or statistically significant effects on the QTc interval, the QRS duration, the PR interval, or heart rate in healthy subjects (n=36).

10.3 Pharmacokinetics

Dapagliflozin and metformin hydrochloride tablets demonstrated comparable bioavailability of dapagliflozin and metformin with co-administered tablets of dapagliflozin and metformin in a four-way crossover comparative bioavailability study under fed and fasted conditions in healthy subjects.

The dapagliflozin and metformin hydrochloride tablets dosage formats (i.e. 5 mg / 850 mg and 5 mg / 1000 mg dapagliflozin / metformin hydrochloride) are proportionally formulated.

Absorption:

Dapagliflozin

Dapagliflozin was rapidly and well absorbed after oral administration and can be administered with food. Geometric mean steady-state dapagliflozin C_{max} and AUC_{τ} values following once daily 10 mg doses of dapagliflozin were 158 ng / mL and 628 ng*h / mL, respectively. 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 proportionally to the increment in dapagliflozin dose. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Food had relatively modest effects on the pharmacokinetics of dapagliflozin in healthy subjects. Administration with a high-fat meal decreased dapagliflozin C_{max} by up to 50% and prolonged T_{max} by approximately 1 hour, but did not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful.

Metformin hydrochloride

Metformin absorption is relatively slow and may extend over 6 hours.

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

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (V_d) ranged between 63-276 l.

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 was 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. 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 was the predominant drug-related component in human plasma, accounting for 42% (based on $AUC_{[0\text{-}12\ h]}$) of total plasma radioactivity, similar to the 39% contribution by parent drug. Based on AUC, no other metabolite accounted for >5% of the total plasma radioactivity at any time point measured. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP-mediated metabolism was a minor clearance pathway in humans.

Metformin hydrochloride

Metformin is not metabolized. Its main sites of concentration are the intestinal mucosa and the salivary glands. The plasma concentration at steady-state ranges about 1 to 2 mcg / mL. Certain drugs may potentiate the effects of metformin. See 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS.

It has been shown that, following a 2 g dose of metformin, the blood level remains under 10 mcg / mL even at the peak, occurring 2 hours after absorption. During the experiments, metformin was shown to be devoid of any notable action in the body, apart from its specific

metabolic activity.

In the healthy animal, metformin lowers blood sugar only at a nearly lethal dose. Different animal species are of unequal sensitivity. On the other hand, the animal with experimental diabetes, is sensitive to a much lower dosage, providing some insulin is still secreted.

The antihyperglycemic action of metformin is probably mediated through insulin. Metformin improves the coefficient of glucose assimilation (K), and the coefficient of insulin efficiency.

In the obese diabetic with hyperinsulinemia, metformin is reported to normalize insulin output. This normalizing effect is concurrent to that of glycemia.

Metformin has little effect on liver glycogen of the healthy animal. In low and average doses, no change occurs. In high doses nearing lethal levels, liver glycogen decreases. This lowering precedes the fall in blood sugar. This reaction represents a defense mechanism tending to mobilize body reserves in order to combat hypoglycemia.

In the diabetic animal with a low liver glycogen reserve, the opposite occurs and metformin builds up glycogen stores of the liver. *In vitro*, on muscular tissue isolated in Warburg's apparatus, metformin increases glucose uptake by the muscle. This action follows an aerobic pathway. Even in high concentration, contrary to phenethyl-biguanide, metformin apparently does not block respiration or change carbohydrate metabolism via the anaerobic pathway.

Metabolites of metformin have not been identified, neither by radio-active nor by chemical methods.

A single Rf spot is always present following radio chromatographic study of urine and always corresponds to that of pure metformin. Administration during 10 consecutive days has not shown any sign of accumulation.

Inhibition of glyconeogenesis has been observed in animals following its stimulation by fasting, cortisol, alcohol or other substrates such as alanine lactate or pyruvate. However, such an effect varies according to the type and dosage of the biguanide used, nutritional state of the animal species and design of experimental model.

This inhibition of glyconeogenesis is observed only in the presence of insulin and it does not appear to play an important role in man.

Inhibition of intestinal absorption of sugars, which is not related to a malabsorption phenomenon has been observed with biguanides under certain experimental conditions in animal and in man. In one study, a 20% retardation of galactose absorption was observed in man receiving metformin. However, such an effect of metformin could not be confirmed in another study in man.

Recent findings appear to indicate that most of the metabolic effects of the biguanides are exerted through a single mechanism, namely inhibition of fatty acid oxidation and of acetyl-CoA generation.

However, inhibition of insulin-stimulated lipogenesis which has also been observed appears to be due to the inhibition of acetyl-CoA carboxylase by the biguanides. Such an effect may explain, at least partly, the weight-reducing effect exerted by these drugs in obese diabetic patients.

Elimination:

Dapagliflozin

Dapagliflozin and related metabolites are primarily eliminated via urinary excretion, of which less than 2% is unchanged dapagliflozin. After administration of 50 mg [14C]-dapagliflozin dose, 96% was recovered, 75% in urine and 21% in feces. In feces, approximately 15% of the dose was excreted as parent drug.

Metformin hydrochloride

Metformin is eliminated in feces and urine. It is rapidly excreted by the kidneys in an unchanged form. The drug is excreted in urine at high renal clearance rate of about 450 mL / min. The initial elimination of metformin is rapid with a half-life varying between 1.7 and 3 hours. The terminal elimination phase accounting for about 4 to 5 % of the absorbed dose is slow with a half-life between 9 and 17 hours.

Special Populations and Conditions

- **Pediatrics (<18 years of age):**

  Dapagliflozin: Auro-Dapagliflozin / Metformin is contraindicated in this patient population. No studies were conducted in the pediatric population.

- **Geriatrics (≥65 years of age):**

  Dapagliflozin: No dosage adjustment for dapagliflozin 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 not to be clinically meaningful.

Metformin hydrochloride: Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients.

- **Sex:**

  Dapagliflozin: No dosage adjustment for dapagliflozin is recommended 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 AUCs in females (n=619) was estimated to be 22% higher than in males (n=634) (90% CI: 117,124).

- **Ethnic Origin:**

  Dapagliflozin: No dosage adjustment for dapagliflozin 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.

- **Hepatic Insufficiency:** Auro-Dapagliflozin / Metformin is contraindicated in patients with clinical or laboratory evidence of hepatic disease. See 2 CONTRAINDICATIONS.

  Dapagliflozin: 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. 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. 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.

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

- **Renal Insufficiency:** Auro-Dapagliflozin / Metformin is contraindicated in patients with severe renal insufficiency due to the metformin component and the risk of lactic acidosis. See 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION.

Dapagliflozin: 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 T2DM and normal renal function. Higher systemic exposures to dapagliflozin in patients with type 2 diabetes mellitus and renal impairment did not result in a correspondingly higher renal glucose clearance or total cumulative glucose excretion. The renal glucose clearance and 24-hour glucose excretion were 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 T2DM 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.

- **Obesity:**

Dapagliflozin: No dosage adjustment for dapagliflozin 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. No dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in T2DM 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, dapagliflozin systemic 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. Based on these findings no dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in T2DM patients with low body weight (<50 kg) is recommended.

11 STORAGE, STABILITY AND DISPOSAL

Store at 15-30°C.

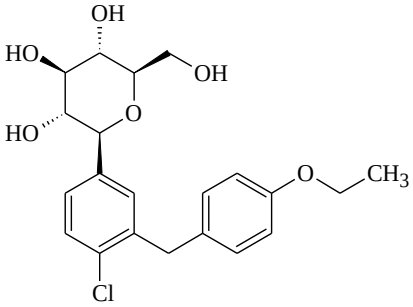
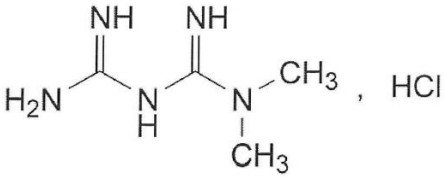
12 SPECIAL HANDLING INSTRUCTIONS

Keep in a safe place out of sight and reach of children.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Drug Substance		
Common Name:	Dapagliflozin	Metformin hydrochloride
Chemical Name:	(2S,3R,4R,5S,6R)-2-[3-(4-ETHOXYBENZYL)-4-CHLOROPHENYL] -6-(HYDROXYMETHYL) TETRAHYDRO-2H-PYRAN-3,4,5-TRIOL	1, 1-Dimethylbiguanide hydrochloride OR N, N-dimethyldiguanide hydrochloride
Molecular Formula and Molecular Mass:	$C_{21}H_{25}ClO_6$ 408.88 g / mol	$C_4H_{11}N_5$, HCl 165.63 g / mol
Structural formula:		
Physicochemical Properties:	White to off-white amorphous powder. Freely soluble in Methanol and Methyl tert-butyl ether; Practically insoluble in n-Heptane and water	Metformin hydrochloride is a white crystalline powder, hygroscopic. Freely soluble in water, slightly soluble in Ethanol (95 %), practically insoluble in Acetone, Chloroform Methylene dichloride and Ether.

14 CLINICAL TRIALS

There have been no clinical studies conducted with dapagliflozin and metformin hydrochloride tablets. Dapagliflozin and metformin hydrochloride tablets demonstrated comparable bioavailability of dapagliflozin and metformin with co-administered tablets of dapagliflozin and metformin in a four-way crossover comparative bioavailability study. See 10.3 Pharmacokinetics.

The co-administration of dapagliflozin and metformin has been studied in patients with type 2 diabetes inadequately controlled on metformin alone or in combination with insulin (see Table 12).

In the dapagliflozin clinical development program, treatment with dapagliflozin in combination with metformin, metformin and glimepiride, metformin and sitagliptin, or metformin and insulin produced clinically relevant and statistically significant improvements in mean change from baseline at Week 24 in HbA1c, fasting plasma glucose (FPG), and 2-hour post-prandial glucose (PPG) (where measured), compared to placebo or control. Across studies that included long- term extensions, the estimated, placebo-adjusted, HbA1c reduction was sustained up to 104 weeks. HbA1c reductions were seen across subgroups including gender, age, race, duration of disease and baseline body mass index (BMI). In addition, patients treated with dapagliflozin compared to placebo or control achieved greater HbA1c reductions in patients with a baseline HbA1c ≥9%.

A large CV outcomes study (DECLARE-TIMI 58) assessed the effect of dapagliflozin on CV outcomes in patients with T2DM with and without established CV disease. Treatment with dapagliflozin 10 mg once daily resulted in a statistically significant and clinically relevant reduction in the risk of hospitalization for HF in patients with type 2 diabetes with and without established CV disease.

14.1 Clinical Trials by Indication

Add-On Combination Therapy with Metformin

Study Design

Table 12 Summary of patient demographics for clinical trials for add-on combination therapy with metformin

Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Multicentre, randomized, double-blind, placebo-controlled	4 groups: dapagliflozin 2.5, 5, or 10 mg or placebo Background therapy: metformin ≥1500 mg / day Oral, 24 weeks + 78 weeks	135 - 137 / 409 / 546 (ST)	53.9	53 / 47
Multicentre, randomized, double-blind, active-controlled	2 groups: dapagliflozin titrated dose of 2.5, 5, or 10 mg or glipizide titrated dose of 5, 10, or 20 mg Background therapy: metformin ≥1500 mg Oral, 52 weeks + 52 weeks + 52 weeks	406 - 408 / 406 / 814 (ST)	58.4	55 / 45
Multicentre, randomized, double-blind, placebo-controlled	4 groups: dapagliflozin 2.5 mg BID, 5 mg BID, 10 mg QD or placebo Background therapy: metformin ≥1500 mg / day Oral, 16 weeks	99-101 / 298 399	57.7	45 / 55

ST=short-term

Study Results

Add-On Combination Therapy with Metformin

A 24-week double-blind, placebo-controlled study was conducted to evaluate dapagliflozin in combination with metformin in patients with type 2 diabetes with inadequate glycemic control (HbA1c ≥7% and ≤10%). Patients on metformin at a dose of at least 1500 mg per day were randomized after completing a 2-week single-blind placebo lead-in period. Following the lead-in period, eligible patients were randomized to dapagliflozin 2.5 mg, dapagliflozin 5 mg, or 10 mg, or placebo in addition to their current dose of metformin.

As shown in Table 13, statistically significant ($p<0.0001$) reductions in HbA1c, FPG and body weight relative to placebo were observed with dapagliflozin 10 mg at Week 24 which were sustained long term.

Dapagliflozin Twice-Daily Add-On to Metformin

Patients with type 2 diabetes and inadequate glycemic control (HbA1c ≥6.5% and ≤10%) on metformin alone were randomized in a 16-week, placebo-controlled study to evaluate dapagliflozin 2.5 mg twice daily and 5 mg twice daily as add-on therapy to metformin. Patients on metformin at a dose of at least 1500 mg per day were randomized following a 4-week single-blind, placebo lead-in period to dapagliflozin 5 mg, dapagliflozin 2.5 mg or placebo twice daily. Study results with dapagliflozin 5 mg or placebo twice daily are summarized in Table 13.

Table 13 Results of placebo-controlled studies of dapagliflozin in add-on combination with metformin up to 24 weeks

	Study D1691C00003 (16-week study)		Study MB102014 (24-week study)	
Efficacy Parameter	**Dapagliflozin 5 mg BID + Metformin N=99†**	**Placebo BID + Metformin N=101†**	**Dapagliflozin 10 mg + Metformin N=135†**	**Placebo + Metformin N=137†**
HbA1c (%)				
Baseline mean	7.79	7.94	7.92	8.11
Change from baseline (adjusted mean‡)	−0.65	−0.30	−0.84	−0.30
Difference from placebo (adjusted mean‡) (95% CI)	−0.35§ (−0.52,−0.18)		−0.54§ (−0.74,−0.34)	
Patients (%) achieving HbA1c <7% adjusted for baseline	38.2¶	21.4	40.6¶	25.9
FPG (mmol / L)				
Baseline mean	8.63	8.77	8.7	9.2
Change from baseline at week 16 / 24 (adjusted mean‡)	-1.42	-0.58	−1.3	−0.3
Difference from placebo (adjusted mean‡) (95% CI)	-0.85§ (-1.19, -0.51)		−1.0§ (-1.4, -0.6)	
Body Weight (kg)				
Baseline mean	93.62	88.82	86.28	87.74
Change from baseline (adjusted mean‡)	-2.74	-0.86	−2.86	−0.89
Difference from placebo (adjusted mean‡) (95% CI)	-1.88# (-2.52, -1.24)		−1.97§ (−2.63, −1.31)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.
† All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.
‡ Least squares mean adjusted for baseline value.
§ p-value <0.0001 vs. placebo + metformin.
¶ p-value <0.05 vs. placebo + metformin.
# absolute body-weight change in kg was analyzed with a nominal p-value (p-value <0.001)

Add-On Therapy with Metformin – Active-Controlled Study versus Glipizide

Patients with type 2 diabetes with inadequate glycemic control (HbA1c >6.5% and ≤10%) were randomized in a 52-week, double-blind, glipizide-controlled non-inferiority study to evaluate dapagliflozin as add-on therapy to metformin. Patients on metformin at a dose of at least 1500 mg per day were randomized following a 2-week placebo lead-in period to glipizide or dapagliflozin (5 mg or 2.5 mg, respectively) and were up-titrated over 18 weeks to optimal glycemic effect (FPG <110 mg / dL, <6.1 mmol / L) or to the highest dose level (up to glipizide 20

mg and dapagliflozin 10 mg) as tolerated by patients. Thereafter, doses were kept constant, except for down-titration to prevent hypoglycemia.
At the end of the titration period, 87% of patients treated with dapagliflozin had been titrated to the maximum study dose (10 mg), versus 73% treated with glipizide (20 mg). As shown in Table 14, treatment with dapagliflozin provided similar reductions in HbA1c from baseline compared to glipizide (with the upper bound of the 95% confidence interval around the between-group difference less than the pre-specified non-inferiority margin of 0.35%). Statistically significant (p<0.0001) reductions in body weight were observed with dapagliflozin compared to glipizide.

Table 14 Results at Week 52 (LOCF*) in an active-controlled study comparing dapagliflozin to glipizide as add-on to metformin

Efficacy Parameter	Dapagliflozin +Metformin N=400†	Glipizide +Metformin N=401†
HbA1c (%)		
Baseline (mean)	7.69	7.74
Change from baseline (adjusted mean‡)	−0.52	−0.52
Difference from Glipizide+Metformin (adjusted mean‡)	0.00¶	
(95% CI)	(−0.11, 0.11)	
Body Weight (kg)		
Baseline (mean)	88.44	87.60
Change from baseline (adjusted mean‡)	−3.22	1.44
Difference from Glipizide+Metformin (adjusted mean‡)	−4.65§	
(95% CI)	(−5.14, −4.17)	

* LOCF: last observation carried forward.
† Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.
‡ Least squares mean adjusted for baseline value.
§ p-value <0.0001.
¶ non-inferior to glipizide + metformin.

Add-On Therapy with Metformin and a Sulfonylurea

Study Design

Table 15 Summary of patient demographics for clinical trials with add-on therapy with metformin and a sulfonylurea

Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Multicentre, randomized, double-blind, placebo- controlled	2 groups: dapagliflozin 10 mg or placebo Background therapy: metformin ≥1500 mg and a sulfonylurea (at maximum tolerated dose and ≥50% of maximum recommended dose) Oral, 24 weeks + 28 weeks	109 / 109 / 218 (ST)	61.0	49 / 51

ST=short-term

Patients with type 2 diabetes and inadequate glycemic control (HbA1c ≥7% and ≤10.5%) participated in a 24-week, double-blind, placebo-controlled study to evaluate dapagliflozin in combination with metformin and a sulfonylurea. Patients on a stable dose of metformin (immediate- or extended-release formulations) ≥1500 mg / day plus maximum tolerated dose, which must be at least half maximum dose, of a sulfonylurea for at least 8 weeks prior to enrolment were randomized after an 8-week placebo lead-in period to dapagliflozin 10 mg or placebo. Dose-titration of dapagliflozin or metformin was not permitted during the 24-week treatment period. Down-titration of sulfonylurea was permitted to prevent hypoglycemia during the treatment period; no up-titration of sulfonylurea was allowed.

Study Results

As shown in Table 16, treatment with dapagliflozin 10 mg in combination with metformin and a sulfonylurea provided significant reductions in HbA1c, FPG and body weight relative to placebo at Week 24 which were sustained long term. At Week 8, statistically significant changes from baseline in systolic blood pressure (SBP, mmHg) of -4.0, and -0.3 were observed for dapagliflozin 10 mg, and placebo, respectively ($p<0.05$).

Table 16 Results of 24-Week (LOCF*) placebo-controlled study of dapagliflozin in combination with metformin and sulfonylurea

Efficacy Parameter	Dapagliflozin 10 mg +Metformin +Sulphonylurea N=108†	Placebo +Metformin +Sulphonylurea N=108†
HbA1c (%)		
Baseline (mean)	8.08	8.24
Change from baseline (adjusted mean‡, ‡‡)	-0.86	-0.17
Difference from placebo (adjusted mean‡, ‡‡)	-0.69§	
(95% CI)	(-0.89, -0.49)	
Patients (%) achieving HbA1c <7% adjusted for baseline	31.8§	11.1
FPG (mmol / L)		
Baseline (mean)	9.3	10.0
Change from baseline at Week 24 (adjusted mean‡)	-1.9	-0.04
Difference from placebo (adjusted mean‡)	-1.86§	

(95% CI)	(−2.4, −1.3)	
Body Weight (kg)		
Baseline (mean)	88.57	90.07
Change from baseline (adjusted mean‡)	-2.65	-0.58
Difference from placebo (adjusted mean‡)	-2.07§	
(95% CI)	(−2.79, −1.35)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.
† Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.
‡ Least squares mean adjusted for baseline value based on ANCOVA model.
‡‡ Least squares mean adjusted for baseline value based on longitudinal repeated measures model.
§ p-value <0.0001 versus placebo.

Add-On Combination Therapy with Sitagliptin in Combination with Metformin

Study Design

Table 17 Summary of patient demographics for clinical trials with add-on combination therapy with sitagliptin in combination with metformin

Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Multicentre, randomized, double-blind, placebo-controlled6	2 groups: dapagliflozin 10 mg or placebo Background therapy: Sitagliptin 100 mg / day (+ / - metformin ≥1500 mg) Oral, 24 weeks + 24 weeks	225 – 226 / 225 / 451 (ST)	55.0	55 / 45

ST=short-term

A total of 452 patients with type 2 diabetes who were drug naive, or who were treated at entry with metformin or sitagliptin alone or in combination, and had inadequate glycemic control (HbA1c ≥7.0% and ≤10.0% at randomization), participated in a 24-week, placebo-controlled study with a 24-week extension.

Patients were stratified based on background metformin use (≥1500 mg / day) and within each stratum were randomized to either dapagliflozin 10 mg plus sitagliptin 100 mg once daily or placebo plus sitagliptin 100 mg once daily. There were 226 patients analysed in the sitagliptin with metformin stratum (N=113 received dapagliflozin 10 mg plus sitagliptin and metformin, N=113 received placebo plus sitagliptin and metformin). Endpoints were tested for dapagliflozin 10 mg versus placebo in the sitagliptin with metformin stratum.

Study Results

As shown in Table 18, statistically significant (p<0.0001) reductions in HbA1c, FPG and body weight relative to placebo were observed with dapagliflozin 10 mg treatment for the sitagliptin

with metformin stratum at Week 24.

Table 18 Results of 24 Week (LOCF*) placebo-controlled study of dapagliflozin in add-on combination with sitagliptin with metformin

Efficacy Parameter	Dapagliflozin 10 mg + Sitagliptin + Metformin N=113†	Placebo + Sitagliptin + Metformin N=113†
HbA1c (%)	N=113	N=113
Baseline mean	7.80	7.87
Change from baseline (adjusted mean‡)	-0.43	-0.02
Difference from placebo (adjusted mean‡)	−0.40§	
(95% CI)	(−0.58, −0.23)	
FPG (mmol / L)	N=112	N=112
Baseline mean	9.21	9.14
Change from baseline at Week 24 (adjusted mean‡)	-1.45	0.17
Difference from placebo (adjusted mean‡)	−1.62§	
(95% CI)	(−2.11, −1.13)	
Body Weight (kg)	N=113	N=113
Baseline mean	93.95	94.17
Change from baseline (adjusted mean‡)	-2.35	-0.47
Difference from placebo (adjusted mean‡)	−1.87§	
(95% CI)	(−2.61, −1.13)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.
† Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.
‡ Least squares mean adjusted for baseline value.
§ p-value <0.0001 versus placebo.

Add-On Combination Therapy with Insulin

Study Design

Table 19 Summary of patient demographics for clinical trials for add-on combination therapy with insulin

Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Multicentre, randomized, double-blind, placebo-controlled10	4 groups: dapagliflozin 2.5, 5, or 10 mg or placebo Background therapy: insulin ≥30 IU/day ± maximum 2 OAD In LT, forced titration of dapagliflozin 5 mg to 10 mg Oral, 24 weeks + 24 weeks + 56 weeks	196 - 212 / 610 / 807 (ST)	59.3	48 / 52

LT=long-term; OAD=Oral anti-diabetic drug; QAM=once in the morning; QPM=once in the evening; ST=short-term

Patients with type 2 diabetes who had inadequate glycemic control (HbA1c ≥7.5% and ≤10.5%) were randomized in a 24-week, double-blind, placebo-controlled study to evaluate dapagliflozin as add-on therapy to insulin. Patients on a stable insulin regimen, with a mean dose of at least 30 IU of injectable insulin per day, for a period of at least 8 weeks prior and on a maximum of two oral antidiabetic medications (OADs) were randomized after completing a 2-week enrolment period to receive dapagliflozin 2.5 mg, dapagliflozin 5 mg, or 10 mg, or placebo in addition to their current dose of insulin and other OADs, if applicable. Patients were stratified according to the presence or absence of background OADs. Up- or down-titration of insulin was only permitted during the treatment phase in patients who failed to meet specific glycemic goals. Subjects on metformin were to be on ≥1500 mg / day.

In this study, 50% (N=392) of patients were on insulin monotherapy at baseline, while 50% were on 1 or 2 OADs in addition to insulin. Of the latter, 80% (N=319) were on a background of insulin and metformin dual therapy. An inadequate number of patients on other OAD combinations were included for evaluative purposes; therefore, use with OAD combinations other than metformin alone is not indicated. In the overall patient sample 48% of patients were taking sliding scale and basal insulin, 35% were taking sliding scale insulin alone and 17% were taking basal insulin. Approximately 88% of patients completed up to Week 24. At Week 24, dapagliflozin 10 mg provided significant improvement in HbA1c and mean insulin dose, and a significant reduction in body weight compared with placebo (Table 20); the effect of dapagliflozin on HbA1c was similar in patients in both strata.

Study Results

Table 20 Results of 24 Week (LOCF*) placebo-controlled study of dapagliflozin in combination with insulin with or without up to 2 oral antidiabetic therapies[§§]

Efficacy Parameter	Dapagliflozin 10 mg + Insulin N=194[†]	Placebo + Insulin N=193[†]
HbA1c (%)		
Baseline mean	8.58	8.46
Change from baseline (adjusted mean[‡])	−0.90	−0.30
Difference from placebo (adjusted mean[‡])	−0.60[§]	
(95% CI)	(−0.74, −0.45)	
FPG (mmol / L)		
Baseline mean	9.6	9.4
Change from baseline (adjusted mean[‡])	−1.2	0.2
Difference from placebo (adjusted mean[‡])	−1.4[§]	
(95% CI)	(−1.9, −0.9)	
Body Weight (kg)		

Efficacy Parameter	Dapagliflozin 10 mg + Insulin N=194†	Placebo + Insulin N=193†
Baseline mean	94.63	94.21
Change from baseline (adjusted mean‡)	−1.67	0.02
Difference from placebo (adjusted mean‡)	−1.68§	
(95% CI)	(−2.19, −1.18)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

† Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.

‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001 versus placebo.

§§ Use with oral antidiabetic combinations other than metformin alone is not indicated.

Cardiovascular Outcomes in Patients with T2DM

Study Design

Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI 58) was an international, multicentre, randomized, double-blind, placebo-controlled, event-driven clinical study conducted to evaluate the effect of dapagliflozin compared with placebo on CV outcomes when added to current background therapy in patients with T2DM and either CV risk factors or established CV disease. The objective was to be evaluated in two steps. First, non-inferiority between dapagliflozin and placebo was evaluated for the primary safety composite endpoint of CV death, myocardial infarction, and ischemic stroke, referred to as Major Adverse Cardiovascular Events (MACE). If non-inferiority for MACE was demonstrated, the study then tested superiority of the dual primary efficacy endpoints of MACE and the composite of hospitalization for heart failure or cardiovascular death, in parallel[2].

All patients had T2DM and either multiple risk factors (at least two additional CV risk factors [age ≥55 years in men or ≥60 years in women and one or more of dyslipidemia, hypertension, or current tobacco use]) without having had a CV event at baseline (primary prevention) or established CV disease (secondary prevention). DECLARE-TIMI 58 was designed to ensure inclusion of a broad patient population. Concomitant antidiabetic and atherosclerotic therapies could be adjusted, at the discretion of investigators according to the standard care for these diseases.

Of 17160 randomized patients, 10186 (59.4%) did not have established CV disease and 6974 (40.6%) had established CV disease. A total of 8582 patients were randomized to dapagliflozin 10 mg, 8578 to placebo, and patients were followed for a mean of 4.1 years. The study was completed by 98.5% of subjects with vital status available for 99.3%, and 13181 (76.8%) subjects completed the study on study drug.

[2] Dual primary efficacy endpoints may be used when success on either endpoint could independently support a conclusion of effectiveness. The dual primary efficacy endpoints in DECLARE-TIMI 58 were tested independently and in parallel. Type 1 error was controlled by splitting the α between the dual primary endpoints

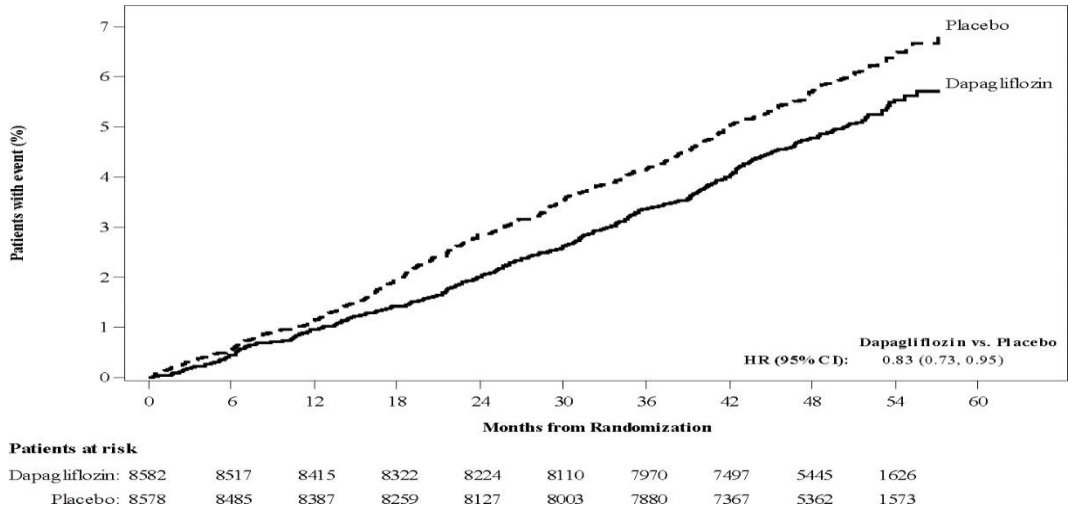
The mean age of the study population was 63.9 years, 37.4% were female, 79.6% were White, 3.5% Black or African-American, and 13.4% Asian. Approximately 46% of patients treated with dapagliflozin were 65 years and older and 6.3% were 75 years and older. In total, 22.4% had diabetes for ≤5 years, and the mean duration of diabetes was 11.9 years. Mean HbA1c was 8.3% and mean BMI was 32.0 kg / m^2. At baseline, 10.0% of patients had a history of HF. Mean eGFR was 85.2 mL / min / 1.73m^2, 7.4% of patients had eGFR <60 mL / min / 1.73m^2 and 45.1% had eGFR ≥60 to <90 mL / min / 1.73m^2. At baseline, 30.3% of patients had micro- or macroalbuminuria (urine albumin to creatinine ratio ≥30 to ≤300 mg / g or >300 mg / g, respectively). Most patients (98.1%) used one or more diabetic medications at baseline: 82.0% of the patients were being treated with metformin, 40.9% with insulin, 42.7% with a sulfonylurea, 16.8% with a DPP4 inhibitor, and 4.4% with a GLP-1 receptor agonist. Approximately 81.3% of patients were treated with ACE inhibitors or ARB, 75.0% with statins, 61.1% with antiplatelet therapy, 55.5% with acetylsalicylic acid, 52.6% with beta-blockers, 34.9% with calcium channel blockers, 22.0% with thiazide diuretics, and 10.5% with loop diuretics.

Study Results

Dapagliflozin demonstrated CV safety (tested against a non-inferiority margin of 1.3 versus placebo for the composite of CV death, MI or ischemic stroke [MACE]; one-sided p<0.001).

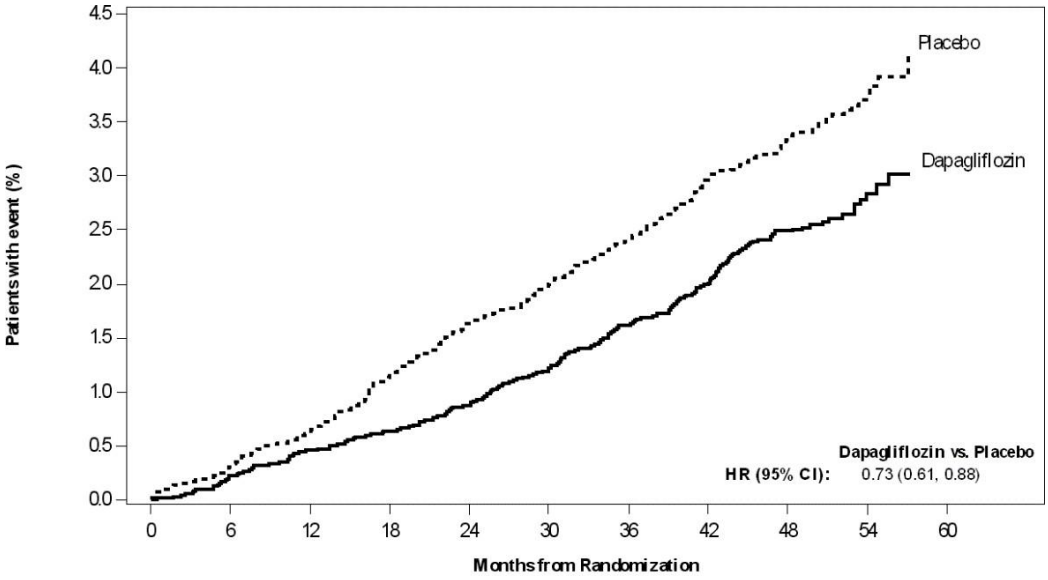
Dapagliflozin was superior to placebo in reducing the incidence of the primary composite endpoint of hospitalization for HF or CV death, representing a 17% reduction in risk (HR 0.83 [95% CI 0.73, 0.95]; p=0.005) (Figure 1). Analyses of the single components suggest that the difference in treatment effect was driven by hospitalization for HF (HR 0.73 [95% CI 0.61, 0.88]), with no clear difference in CV death (HR 0.98 [95% CI 0.82 to 1.17]) (Figure 2).

Figure 1 Time to first occurrence of hospitalization for heart failure or cardiovascular death in the DECLARE-TIMI 58 study



Patients at risk is the number of patients at risk at the beginning of the period. CI Confidence interval, HR Hazard ratio.

Figure 2 Time to First Occurrence of Hospitalization for Heart Failure in the DECLARE-TIMI 58 Study



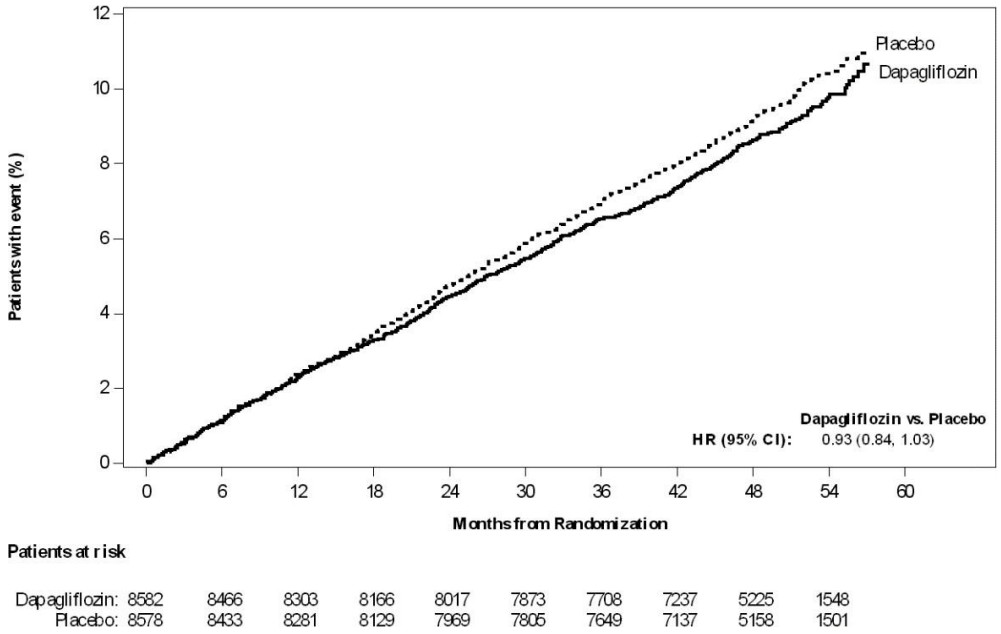
Patients at risk

Dapagliflozin:	8582	8509	8403	8315	8218	8101	7965	7489	5439	1626
Placebo:	8578	8482	8380	8256	8121	7998	7874	7360	5358	1572

Patients at risk is the number of patients at risk at the beginning of the period. CI Confidence interval, HR Hazard ratio.

Superiority of dapagliflozin over placebo was not demonstrated for MACE (HR 0.93 [95% CI 0.84, 1.03]; p=0.172) (Figure 3, Table 21). Analyses of the single components of MACE show that the incidence of MI was numerically lower in the dapagliflozin group compared with the placebo group (HR 0.89 [95% CI 0.77 to 1.01]), with no clear difference observed for CV death or ischemic stroke.

Figure 3 Time to First Occurrence of MACE in the DECLARE-TIMI 58 Study



Patients at risk is the number of patients at risk at the beginning of the period. CI Confidence interval, HR Hazard ratio.

As MACE was not statistically significant, the secondary endpoints renal composite (time to first confirmed sustained eGFR decrease, ESRD, renal or CV death) and all-cause mortality were not tested as part of the confirmatory testing.

Table 21 Treatment Effects for the Composite Endpoints* and Their Components in the DECLARE Study

	Patients with events, n (%)			
Efficacy Parameter	**Dapagliflozin 10 mg N=8582**	**Placebo N=8578**	**Hazard ratio (95% CI)†**	**p-value‡**
Composite of Hospitalization for HF, CV Death	417 (4.9)	496 (5.8)	0.83 (0.73, 0.95)	0.005
Hospitalization for HF§	212 (2.5)	286 (3.3)	0.73 (0.61, 0.88)	<0.001
CV Death§	245 (2.9)	249 (2.9)	0.98 (0.82, 1.17)	0.830
Composite Endpoint of CV Death, MI, Ischemic Stroke	756 (8.8)	803 (9.4)	0.93 (0.84, 1.03)	0.172
CV Death§	245 (2.9)	249 (2.9)	0.98 (0.82, 1.17)	0.830
Myocardial Infarction§	393 (4.6)	441 (5.1)	0.89 (0.77, 1.01)	0.080
Ischemic Stroke§	235 (2.7)	231 (2.7)	1.01 (0.84, 1.21)	0.916

Renal Composite Endpoint[§§]	370 (4.3)	480 (5.6)	0.76 (0.67, 0.87)	
All-Cause Mortality	529 (6.2)	570 (6.6)	0.93 (0.82, 1.04)	

N=Number of patients, CI=Confidence interval, HF=Heart Failure, CV=Cardiovascular, MI=Myocardial infarction, eGFR=estimated glomerular filtration rate ESRD=End stage renal disease

* Full analysis set.

† Hazard ratio, CI, and p-values for each efficacy parameter calculated from Cox proportional hazards model (Wald test) based on time to first occurrence, stratified by baseline CV risk and hematuria with treatment as a model term.

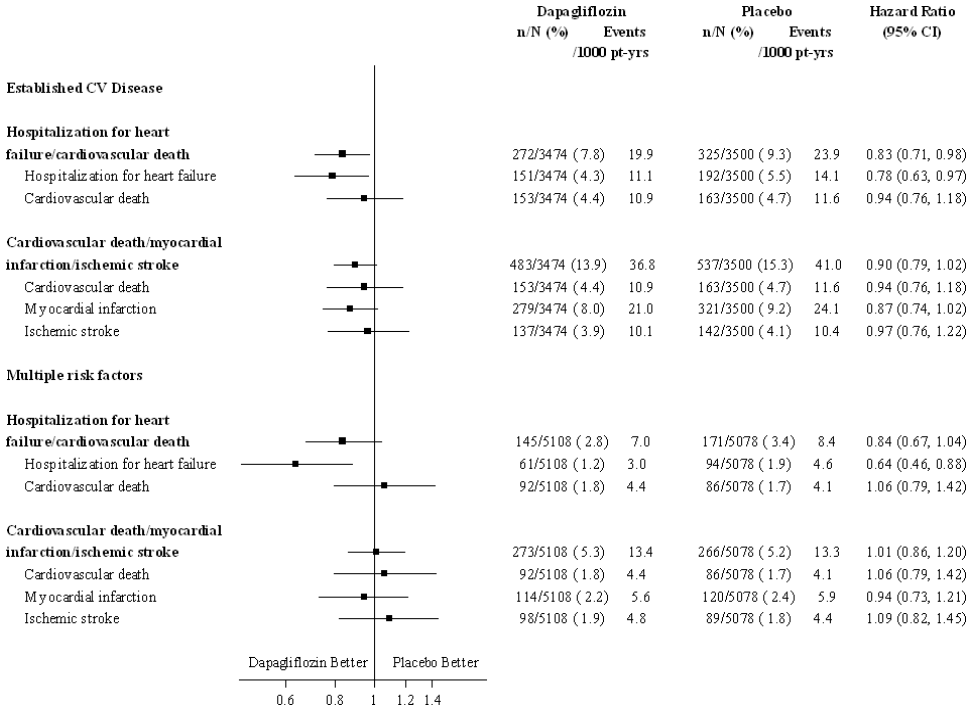
‡ Superiority versus placebo for hospitalization for heart failure or CV death, and superiority versus placebo for MACE were tested in parallel following closed testing procedure at α = 0.0231 (two- sided). As the composite of hospitalization for heart failure and CV was statistically significant, the full α was recycled to test MACE at α=0.0462 (two-sided). As MACE was not statistically significant, the secondary endpoints of renal composite and all-cause mortality were not tested as part of the confirmatory testing procedure.

§ The components of the composite endpoints were exploratory variables.

§§ Confirmed sustained ≥40% decrease in eGFR to eGFR <60 ml / min / 1.73m^2, ESRD (dialysis ≥90 days or kidney transplantation, confirmed sustained eGFR <15 ml / min / 1.73m^2), renal or CV death.

Patients in DECLARE-TIMI 58 were stratified by CV risk category (CV risk factors or established CV disease). The benefit of dapagliflozin over placebo in reducing the risk of hospitalization for heart failure was observed both in patients with and without established CV disease (Figure 4) and was consistent across key subgroups including age (>65 and ≥65 years, and <75 and ≥75 years), gender, renal function (eGFR), and region. There was a trend towards an effect of dapagliflozin on MACE in patients with established CV disease at baseline and neutral results in patients with CV risk factors (Figure 4).

Figure 4 Cardiovascular Outcomes in Patients with and without Established CV Disease in the DECLARE-TIMI 58 Study



Time to first event was analyzed in a Cox proportional hazards model.
CI=confidence interval

Use in Patients with Type 2 Diabetes and Cardiovascular Disease (CVD)

Study Design

In two 24-week, placebo-controlled studies with 80-week extension periods, a total of 1876 patients with type 2 diabetes and CVD were randomized and treated with dapagliflozin 10 mg (N=935) or placebo (N=941).

Patients had established CVD and inadequate glycemic control (HbA1c ≥7.0% and ≤10.0%), despite stable treatment with OADs and / or insulin. Ninety-six percent of patients treated with dapagliflozin 10 mg had hypertension at entry, and the most common qualifying CV events were coronary heart disease (76%) or stroke (20%). Approximately 19% of patients received loop diuretics during the studies and 14% had congestive heart failure (1% had NYHA Class III). Approximately 37% of patients received metformin plus one additional OAD (sulfonylurea, thiazolidinedione, DPP4-inhibitor, or other OAD with or without insulin at entry), 38% received insulin plus at least one OAD, and 18% received insulin alone.

Study Results

For both studies, at Week 24 treatment with dapagliflozin 10 mg provided significant improvement in HbA1c compared with placebo (Table 22). Significant reductions in total body weight and seated systolic blood pressure were also seen in patients treated with dapagliflozin

10 mg compared with placebo. For both studies, reductions in HbA1c and body weight were generally maintained at Week 52 and Week 104.

Table 22 Results at Week 24 (LOCF*) in Two Placebo-Controlled Studies Comparing Dapagliflozin to Placebo in Patients with Type 2 Diabetes and Cardiovascular Disease

	Study D1690C00018		Study D1690C00019	
Efficacy Parameter	**Dapagliflozin 10 mg + Usual Treatment N=455†**	**Placebo + Usual Treatment N=459†**	**Dapagliflozin 10 mg + Usual Treatment N=480†**	**Placebo+ Usual Treatment N=482†**
HbA1c (%)				
Baseline mean	8.18	8.08	8.04	8.07
Change from baseline (adjusted mean‡)	−0.38	0.08	−0.33	0.07
Difference from placebo (adjusted mean‡) (95% CI)	−0.46§ (−0.56, −0.37)		−0.40§ (−0.50, −0.30)	
Body Weight (kg)				
Baseline mean	92.63	93.59	94.53	93.22
Change from baseline (adjusted percent‡)	−2.56	−0.30	−2.53	−0.61
Difference from placebo (adjusted percent‡) (95% CI)	−2.27§ (−2.64, −1.89)		−1.93§ (−2.31, −1.54)	

* LOCF: last observation carried forward.

† Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.

‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001.

Blood Pressure

At Week 24 across 11 clinical studies, treatment with dapagliflozin 10 mg decreased the placebo-corrected systolic blood pressure an average of -1.3 to -5.3 mmHg from baseline in all of the monotherapy and placebo-controlled add-on combination therapy studies.

Bone Mineral Density and Body Composition in Type 2 Diabetic Patients[3]

A 24-week study in 182 diabetic subjects using dual energy x-ray absorptiometry (DXA) to evaluate body composition, demonstrated reductions with dapagliflozin 10 mg plus metformin compared with placebo plus metformin, respectively in body weight and body fat mass, rather

[3] Dual primary efficacy endpoints may be used when success on either endpoint could independently support a conclusion of effectiveness. The dual primary efficacy endpoints in DECLARE-TIMI 58 were tested independently and in parallel. Type 1 error was controlled by splitting the α between the dual primary endpoints.

than lean tissue or fluid loss; with a significant interaction for gender with greater weight loss for males than females. Treatment with dapagliflozin 10 mg plus metformin showed a numerical decrease in visceral adipose tissue compared with placebo plus metformin treatment (see Table 23).

In an extension of this study to week 102 there was no change in bone mineral density for the lumbar spine, femoral neck, or total hip seen in either treatment group (mean decrease from baseline for all anatomical regions <0.5%).

Table 23 Results of 24 Week (LOCF*) Placebo-Controlled Study with Dapagliflozin in Combination with Metformin on Body Weight in Type 2 Diabetes Mellitus Subjects Inadequately-Controlled on Metformin

Efficacy Parameter	Dapagliflozin 10 mg + Metformin N=89†	Placebo + Metformin N=91†
Total Body Weight (kg)		
Baseline mean	92.06	90.91
Week 24 LOCF mean	89.06	90.01
Change from baseline (adjusted mean‡)	-2.96	-0.88
Difference from placebo (adjusted mean‡)	−2.08β	
(95% CI)	(−2.84, −1.31)	
Gender		
Male	N=49	N=51
Baseline mean	98.09	95.89
Week 24 LOCF mean	94.40	95.01
Change from baseline (adjusted mean‡)	-3.56	-0.80
Difference from placebo (adjusted mean‡)	−2.76§	
(95% CI)	(−3.78, −1.74)	
Female	N=40	N=40
Baseline mean	84.68	84.56
Week 24 LOCF mean	82.52	83.63
Change from baseline (adjusted mean‡)	-2.28	-1.06
Difference from placebo (adjusted mean‡)	−1.22§	
(95% CI)	(−2.36, −0.08)	
Body Fat Mass (kg)		
Baseline mean	33.56	33.08
Week 24 LOCF mean	31.29	32.32
Change from baseline (adjusted mean‡)	-2.22	-0.74
Difference from placebo (adjusted mean‡)	−1.48β	
(95% CI)	(−2.22, −0.74)	

* LOCF: last observation carried forward.

† Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.

‡ Least squares mean adjusted for baseline value.

β p-value <0.0001.

§ p-value <0.0481.

14.2 Comparative Bioavailability Studies

A randomized, two-way, single-dose, cross-over, comparative bioavailability study of Auro-Dapagliflozin / Metformin tablets 5 mg / 1000 mg (Auro Pharma Inc.) with [Pr]XIGDUO® tablets 5 mg / 1000 mg (AstraZeneca Canada Inc.) was conducted in healthy, adult, human subjects under fasting conditions. Comparative bioavailability data from 48 subjects that were included in the statistical analysis is presented in the following tables.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Dapagliflozin (1 X 5 mg dapagliflozin / 1000 mg metformin) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h / mL)	298.6 308.9 (27.1)	296.2 304.4 (24.4)	100.8	98.5 - 103.2
AUC_I (ng·h / mL)	312.3 322.8 (26.6)	310.1 318.6 (24.5)	100.7	98.4 - 103.1
C_{max} (ng / mL)	69.2 73.4 (42.1)	67.7 69.9 (27.9)	102.2	94.6 - 110.4
T_{max}[3] (h)	2.0 (0.5 - 3.0)	2.3 (0.5 - 4.0)		
$t_{1/2}$[4] (h)	7.4 (52.9)	7.4 (44.8)		

[1] Auro-Dapagliflozin / Metformin (dapagliflozin / metformin hydrochloride) tablets, 5 mg / 1000 mg (Auro Pharma Inc.)
[2] [Pr]XIGDUO® (dapagliflozin as dapagliflozin propanediol monohydrate / metformin hydrochloride) tablets, 5 mg / 1000 mg (AstraZeneca Canada Inc.)
[3] Expressed as the median (range) only
[4] Expressed as arithmetic mean (CV %) only

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Metformin (1 X 5 mg dapagliflozin / 1000 mg metformin) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng·h / mL)	14740.5 15363.2 (27.9)	14362.8 14779.8 (23.7)	102.6	97.5 - 108.1
AUC_I (ng·h / mL)	14950.6 15567.7 (27.6)	14604.8 15022.8 (23.5)	102.4	97.3 - 107.7
C_{max} (ng / mL)	2471.2 2598.1 (31.6)	2311.8 2379.7 (25.2)	106.9	100.6 - 113.6
T_{max}[3] (h)	1.5 (0.7 - 4.0)	2.0 (1.0 - 4.0)		
$t_{1/2}$[4] (h)	4.9 (37.7)	5.2 (57.7)		

[1] Auro-Dapagliflozin / Metformin (dapagliflozin / metformin hydrochloride) tablets, 5 mg / 1000 mg (Auro Pharma Inc.)
[2] [Pr]XIGDUO® (dapagliflozin as dapagliflozin propanediol monohydrate / metformin hydrochloride) tablets, 5 mg / 1000 mg (AstraZeneca Canada Inc.)
[3] Expressed as the median (range) only
[4] Expressed as the arithmetic mean (CV %) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute and repeat-dose toxicity

Dapagliflozin and Metformin hydrochloride

A 3-month oral repeat-dose combination toxicity study in rats was conducted with the dapagliflozin and metformin fixed-dose combination. No toxicity was observed at AUC exposures 52 and 1.4 times the MRHD for dapagliflozin and metformin, respectively. The non-clinical findings are aligned with the findings in studies with dapagliflozin and metformin individually.

Dapagliflozin

Dapagliflozin demonstrated low acute toxicity. The minimum lethal doses of dapagliflozin following single oral administration were 750 mg / kg in rats and 3000 mg / kg in mice.

Dapagliflozin was well tolerated when given orally to rats for up to 6 months at doses of ≤25 mg / kg / day (up to 340× the human exposures (AUC) at the maximum recommended human dose (MRHD) of 10 mg / day resulting in AUC 0.465 mcg.h / mL, and in dogs for up to 12 months at doses of ≤120 mg / kg / day (up to 3300× the MRHD). In rats, renal lesions (mainly cortical tubular dilatation, medullary tubular dilatation, degeneration, necrosis, mineralization, and reactive hyperplasia, and exacerbation of chronic progressive nephropathy), increased trabecular bone, and tissue mineralization (associated with increased serum calcium), were observed at high- exposure multiples (≥2100× the MRHD). Despite achieving exposure multiples of ≥3200× the human exposure at the MRHD, there was no dose-limiting or target organ toxicities identified in the 12-month dog study.

Carcinogenicity:

Dapagliflozin

Dapagliflozin did not induce tumors in either mice or rats at any of the doses evaluated in two-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 equivalent to AUC exposure multiples of approximately 72× (males) and 105× (females) the human AUC at the MRHD. In rats, AUC exposures were approximately 131× (males) and 186× (females) the human AUC at the MRHD. In a 6-month bladder tumour initiation-promotion study in rats with dapagliflozin (7 times MRHD), the results showed that dapagliflozin does not act as promoter or progressor of bladder cancer.

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 mg / kg / day and 1500 mg / kg / day, respectively. These doses are both approximately 4 times the maximum recommended human daily dose 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.

Genotoxicity:

Dapagliflozin

Dapagliflozin was negative in the Ames mutagenicity assay, and was positive in *in vitro*

clastogenicity assays but only in the presence of S9 activation and at concentrations ≥100 mcg / mL. Dapagliflozin was negative for clastogenicity in vivo in a series of studies evaluating micronuclei or DNA repair in rats at exposure multiples >2100× the human exposure at the MRHD. These studies, along with the absence of tumor findings in the rat and mouse carcinogenicity studies, support that dapagliflozin does not represent a genotoxic risk to humans.

Metformin hydrochloride

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.

Reproductive and Developmental Toxicology:

Dapagliflozin

In a study of fertility and early embryonic development in rats, dapagliflozin had no effects on mating, fertility, or early embryonic development in treated males or females at exposure multiples up to 998× and 1708× the MHRD in males and females, respectively.

In a pre- and postnatal development study, maternal rats were dosed from gestation day (GD) 6 through lactation day 21 at 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× and 137×, respectively, the human values at the MHRD). Dose-related reductions in pup body weights were observed at doses ≥15 mg / kg / day (pup exposures were ≥29× the human values at the MRHD). Maternal toxicity was evident only at 75 mg / kg / day, and limited to transient reductions in body weight and food consumption at dose initiation. The no-adverse- effect level (NOAEL) for developmental toxicity was 1 mg / kg / day (maternal exposure was 19× the human value at the MRHD).

In embryo-fetal development studies in rats and rabbits, dapagliflozin was administered for intervals coinciding with the major periods of organogenesis in each species. Neither maternal nor developmental toxicities were observed in rabbits up to the highest dose of 180 mg / kg / day (184× the MRHD). In rats, dapagliflozin was not teratogenic at doses up to 75 mg / kg / day (1441× the MRHD). Doses ≥150 mg / kg / day (≥2344× the MRHD) were associated with both maternal and developmental toxicities. Developmental toxicity consisted of reduced fetal body weights, increased embryo-fetal lethality, and increased incidences of fetal malformations and skeletal variations. Malformations included great vessel malformations, fused ribs and vertebral centras, and duplicated manubria and sternal centra. Variations were primarily reduced ossifications.

Metformin hydrochloride

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg / kg / day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

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 maximum recommended human daily dose 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.

Juvenile Toxicity

Dapagliflozin

In a juvenile toxicity study, when dapagliflozin was dosed directly to young rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg / kg / day, increased kidney weights and renal pelvic and tubular dilatations were reported at all dose levels; pup exposures at the lowest dose tested were ≥15× the MRHD. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1-month recovery period.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrXIGDUO® Tablets, 5 mg / 850 mg, 5 mg / 1000 mg, submission control 288937, Product Monograph, AstraZeneca Canada Inc. (JAN 22, 2025)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]Auro-Dapagliflozin / Metformin

Dapagliflozin and metformin hydrochloride tablets

Read this carefully before you start taking **Auro-Dapagliflozin / Metformin** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Auro-Dapagliflozin / Metformin**.

Serious Warnings and Precautions

Lactic Acidosis:

- Auro-Dapagliflozin / Metformin contains metformin and may cause lactic acidosis. This is a serious condition when there is too much lactic acid in your body. It can cause death. The risk of lactic acidosis is higher if you:
  - have liver, kidney or heart problems, including heart failure.
  - drink a lot of alcohol. Do not drink a lot of alcohol while taking Auro-Dapagliflozin / Metformin.
  - are 80 years of age or older.

- **Stop taking Auro-Dapagliflozin / Metformin right away** and talk to your healthcare professional if you have any of the following symptoms:
  - discomfort, difficulty breathing, nausea, vomiting, diarrhea, stomach or muscle pain, extreme tiredness, weakness, feeling cold, low blood pressure or slow or irregular heartbeat
- Auro-Dapagliflozin / Metformin can also cause diarrhea, nausea, upset stomach, bloating, gas or loss of appetite. If any of these side effects come back after you are on the same dose of Auro-Dapagliflozin / Metformin for many days or weeks, tell your healthcare professional right away. These symptoms may be due to lactic acidosis.
- Lactic acidosis must be treated in the hospital. Your healthcare professional will decide the best treatment options for you.

Diabetic Ketoacidosis:

- Diabetic ketoacidosis (DKA) can happen while you are taking Auro-Dapagliflozin / Metformin. It is a serious and life-threatening condition, which may need urgent hospital care. Some cases of DKA have led to death. DKA can happen to diabetic patients with normal or high blood sugar levels.
- In DKA your body produces high levels of blood acids called ketones. It occurs because

your body does not have enough insulin.
- Seek medical help and **stop taking Auro-Dapagliflozin / Metformin right away** if you have any of the following symptoms (even if your blood sugar levels are normal):
  - difficulty breathing, nausea, vomiting, stomach pain, loss of appetite, confusion, feeling very thirsty, feeling unusually tired, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat.
- Do not use Auro-Dapagliflozin / Metformin if you have:
  - DKA or a history of DKA
  - type 1 diabetes

What is Auro-Dapagliflozin / Metformin used for?

Auro-Dapagliflozin / Metformin is used along with diet and exercise to:

- control blood sugar levels in adults with type 2 diabetes. Auro-Dapagliflozin / Metformin can be used in patients taking:

  - dapagliflozin and metformin as separate tablets, or
  - dapagliflozin, metformin and a sulfonylurea, or
  - dapagliflozin, metformin and sitagliptin, or
  - dapagliflozin, metformin and insulin.

How does Auro-Dapagliflozin / Metformin work?

Auro-Dapagliflozin / Metformin contains dapagliflozin and metformin hydrochloride.

- Dapagliflozin removes excess sugar from the body through the urine.
- Metformin helps your body respond better to the insulin it makes naturally. It helps to lower the amount of sugar made by the liver and lower the amount of sugar moved from the gut into the blood.

What are the ingredients in Auro-Dapagliflozin / Metformin?

Medicinal ingredients: dapagliflozin and metformin hydrochloride.

Non-medicinal ingredients:
Lactose monohydrate, Hydroxy propylcellulose and Magnesium stearate
For 5mg / 850mg film coating contains: Opadry AMB II High Performance Moisture Barrier Film Coating 88A570010 Beige.
For 5mg / 1000mg film coating contains: Opadry AMB II High Performance Moisture Barrier Film Coating 88A520050 Yellow.

Auro-Dapagliflozin / Metformin comes in the following dosage forms:

- dapagliflozin 5 mg / metformin hydrochloride 850 mg
- dapagliflozin 5 mg / metformin hydrochloride 1000 mg

Do not use Auro-Dapagliflozin / Metformin if you:

- have unstable and / or insulin-dependent (Type I) diabetes mellitus
- have or have a history of metabolic acidosis (including diabetic ketoacidosis / DKA or ketoacidosis, with or without coma)
- have a history of lactic acidosis (too much acid in the blood)
- have or ever had severe kidney or liver problems, or are on dialysis
- regularly drink large amounts of alcohol all the time or short-term 'binge'
- are going to get an injection of dyes (iodinated contrast materials) for medical imaging
- have severe problems with your blood circulation or heart problems that can cause hypoxemia (low oxygen in the blood)
- are stressed and have a severe infection, or are experiencing trauma
- will have surgery or are recovering from surgery
- suffer from severe dehydration (have lost a lot of water from your body) or shock
- are allergic (hypersensitive) to dapagliflozin, metformin hydrochloride or any of the ingredients listed in this medicine or component of the container
- are pregnant or planning to become pregnant
- are breast-feeding or plan to breast-feed

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Auro-Dapagliflozin / Metformin. Talk about any health conditions or problems you may have, including if you:

- have an increased risk of developing DKA, including if you:
  - are dehydrated or suffer from excessive vomiting, diarrhea, or sweating
  - are on a very low carbohydrate diet
  - have been fasting for a while
  - need to have a procedure that requires long periods of fasting
  - are eating less, or there is a change in your diet
  - drink a lot of alcohol
  - have / have had problems with your pancreas, including pancreatitis or surgery on your pancreas
  - are or going to be hospitalized for major surgery, serious infection or serious medical illnesses. Your healthcare professional may stop your treatment with Auro-Dapagliflozin / Metformin. Talk to your healthcare professional about when to stop taking Auro-Dapagliflozin / Metformin and when to start taking it again.
  - have a sudden reduction in your insulin dose
  - have a history of DKA

- are older than 65 years of age
- have a history or had liver or kidney problems
- have stomach problems
- have hormone problems (adrenal (found on top of your kidneys) or pituitary glands (found in your brain))
- have low blood sugar
- have low vitamin B12 or folic acid levels
- have low blood pressure
- have or had heart problems (like heart failure, heart attack or heart disease)
- are taking medicines to lower your blood pressure, including diuretics, known as water pills. If you take Auro-Dapagliflozin / Metformin with these medicines, it can increase the risk of dehydration.
- are taking medicines to lower blood sugar. Taking Auro-Dapagliflozin / Metformin with any of these medications can increase the risk of having low blood sugar (hypoglycemia).
- have a history of yeast infection of the vagina or penis
- have a history of urinary tract infections
- have had a recent stroke
- are dehydrated
- are scheduled for x-ray or scanning procedures
- are 80 years of age or older and have NOT had your kidney function tested
- have had an allergic reaction to other medicines used to treat type 2 diabetes

Other warnings you should know about:

Auro-Dapagliflozin / Metformin can cause serious side effects, including:

- **Vitamin B12 levels:** Auro-Dapagliflozin / Metformin can cause your vitamin B12 levels to be lower. This could cause peripheral neuropathy (nerve damage) or anemia (low red blood cells).

- **Hypoglycemia (low blood sugar):** Auro-Dapagliflozin / Metformin rarely causes hypoglycemia (low blood sugar) by itself. Hypoglycemia can happen if you:

  - take other medicines to lower blood sugar. Your healthcare professional may adjust your dose of insulin or other antidiabetic medicines when taking Auro-Dapagliflozin / Metformin. This is to help you keep your blood sugar levels within the normal range during your treatment.
  - do not eat enough
  - drink alcohol
  - have hormone (adrenal or pituitary gland) or liver problems

- **Thyroid problems (hypothyroidism):** tell your healthcare professional if you have thyroid problems or if you are being treated with levothyroxine (a drug used to treat thyroid

problems). Your healthcare professional will monitor your thyroid health.

- **Yeast infection**: Auro-Dapagliflozin / Metformin increases your risk of getting a yeast infection of the vagina or penis, especially if you have had them in the past.

- **Urinary tract infection, including urosepsis:** Urosepsis is a severe infection that spreads from the urinary tract throughout the body. This condition is serious and may be life-threatening if left untreated. If you experience signs of this condition, stop taking Auro-Dapagliflozin / Metformin right away and seek immediate medical help.

- **Fournier's gangrene:** This is a serious infection affecting the soft tissue around the groin. Rare cases of Fournier's gangrene have been reported in patients with type 2 diabetes while taking SGLT2 inhibitors like Auro-Dapagliflozin / Metformin. This condition is serious and may be life threatening. If you experience signs of this condition, stop taking Auro-Dapagliflozin / Metformin right away and seek immediate medical help.

See the Serious side effects and what to do about them table, below, for more information on these and other serious side effects.

Pregnancy and breast-feeding: Female patients:
- Do not take Auro-Dapagliflozin / Metformin if you are pregnant.
- Tell your healthcare professional right away if you plan to become pregnant or think you may be pregnant during your treatment with Auro-Dapagliflozin / Metformin. It is not known if Auro-Dapagliflozin / Metformin will harm your unborn baby.
- Do not breast-feed while you are taking Auro-Dapagliflozin / Metformin. It is not known if Auro-Dapagliflozin / Metformin will pass into your breast milk. Talk to your healthcare professional if you would like to breast-feed.

Children and adolescents: Auro-Dapagliflozin / Metformin is not to be used in children and adolescents under 18 years of age.

Patients older than 65 years old: You should not take Auro-Dapagliflozin / Metformin if you are older than 80 years old unless certain tests are done to check your kidney health. Auro-Dapagliflozin / Metformin should be used with care as age increases because older patients are more likely to have kidney problems. Your healthcare professional may do certain tests to check your kidney health.

Driving and using machines: Before doing tasks that require special attention, wait until you know how you respond to Auro-Dapagliflozin / Metformin. Dizziness, light-headedness or fainting can happen, particularly when Auro-Dapagliflozin / Metformin is taken with insulin or other antidiabetic medicines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Auro-Dapagliflozin / Metformin:

- Medicines used to treat diabetes (lower blood sugar levels), like glyburide, gliclazide or glimepiride, or insulin. If you take Auro-Dapagliflozin / Metformin with any of these medicines, it can increase the risk of low blood sugar.
- Nifedipine, ACE-inhibitors like enalapril, lisinopril and quinapril used to treat high blood pressure, chest pain and Raynaud's phenomenon
- Lithium, used to treat bipolar disorder
- Medicines used to treat irregular heartbeats like procainamide, quinidine
- Medicines used to treat heart failure and irregular heartbeats like digoxin
- Medicines used to treat pain like morphine and NSAIDs (nonsteroidal anti-inflammatory drugs)
- Medicines used to lower stomach acid like ranitidine and cimetidine
- Medicine used to treat malaria like quinine
- Medicines used to treat bacterial infections (antibiotics) like trimethoprim, vancomycin
- Medicines used as "blood thinners" like phenprocoumon or other Vitamin K anticoagulants
- Medicines used to lower the extra fluid in your body (diuretics / water pills), like furosemide, amiloride, triamterene
- Other drugs that tend to produce high blood sugar (hyperglycemia) and may lead to a loss of blood sugar control. Examples include:
  - Thiazide and other diuretics (used to lower extra fluid in your body)
  - Phenytoin, used to treat epilepsy
  - Nicotinic Acid, used to prevent and treat low niacin
  - Isoniazid, used to treat tuberculosis
  - Corticosteroids (anti-inflammatory drugs) like prednisone
  - Phenothiazines, used to treat mental and emotional disorders
  - Thyroid drugs, like levothyroxine
  - Female hormones like estrogens or estrogens plus progestogen
  - Oral birth control pills
  - Sympathomimetics, used to stimulate the sympathetic nervous system
  - Medicines used to lower blood pressure, like amlodipine, felodipine, verapamil and diltiazem
  - Medicines for asthma such as salbutamol or formoterol

How to take Auro-Dapagliflozin / Metformin:

- Take exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Take by mouth with a meal. Swallow tablets whole with a glass of water.
- Do not crush or break tablets.

Your healthcare professional may temporarily stop your Auro-Dapagliflozin / Metformin treatment:

- for at least 3 days before, and a period of time after, certain types of surgery, or procedures associated with long periods of fasting.
- when you are hospitalized for a serious infection or illness.

If Auro-Dapagliflozin / Metformin is stopped, your healthcare professional will:

- continue to monitor for signs or symptoms of DKA.
- tell you when to start taking Auro-Dapagliflozin / Metformin again.

Usual dose:

- **Adults 18 years and older:** Your healthcare professional will decide on the best dosage for you based on your condition.

- Your healthcare professional may lower your dose, stop your treatment for a period of time or recommend that you stop treatment completely. This may happen if you:
  - experience serious side effects, or
  - your disease gets worse.

Overdose:

If you think you, or a person you are caring for, have taken too much Auro-Dapagliflozin / Metformin, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

If you have taken more Auro-Dapagliflozin / Metformin than you should have, you may get lactic acidosis. Symptoms include: rapid or trouble breathing, stomach pain, nausea and vomiting. These are followed by diarrhea, drowsiness, weakness, dizziness or headache.

Missed Dose:

If you miss a dose of Auro-Dapagliflozin / Metformin: wait for the next dose at the usual time. Do not take a double dose.

What are possible side effects from using Auro-Dapagliflozin / Metformin?

These are not all the possible side effects you may have when taking Auro-Dapagliflozin / Metformin. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- sore throat, cough
- the flu (fever, tiredness, body aches)
- stuffy or runny nose
- constipation, bloating, gas
- loss of appetite
- weight loss
- metallic taste
- diarrhea
- upset stomach
- nausea, vomiting
- back, joint or abdominal pain
- pain in the arms, legs, hands or feet
- headache
- skin problems: skin reaction, rash, itchy skin
- low vitamin B12 (vitamin B12 deficiency)

If any of these affects you severely, tell your healthcare professional.

Auro-Dapagliflozin / Metformin can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and interpret the results. They may check your blood fat and red blood cell levels in your blood. They may also check your liver, kidney and thyroid health.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Urinary tract infection: pain, or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine		√	
Yeast infection of penis: red, swollen, itchy head of penis; thick, lumpy discharge under foreskin; unpleasant odour; difficulty retracting foreskin; pain passing urine or during sex	√		
Yeast infection of vagina: severe itching, burning, soreness, irritation, and a whitish or whitish- gray cottage cheese-like discharge	√		
UNCOMMON			

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Hypoglycemia (low blood sugar): shaking, sweating, rapid heartbeat, change in vision, hunger, headache and change in mood		√	
Hypotension (low blood pressure): **dizziness**, fainting, light-headedness; may occur when you go from lying to sitting to standing up		√	
Volume depletion (loss of needed fluids from the body; dehydration): dry or sticky mouth, headache, dizziness or urinating less often than normal		√	
RARE			
Diabetic ketoacidosis (DKA): difficulty breathing, nausea, vomiting, stomach pain, loss of appetite, confusion, feeling very thirsty, feeling unusual tiredness, a sweet smell to the breath, a sweet or metallic taste in the mouth or a different odour to urine or sweat			√
Encephalopathy (disease of the brain that severely alters thinking): Possible neurological symptoms include: muscle weakness in one area, poor decision-making or concentration, involuntary twitching, trembling, difficulty speaking or swallowing, seizures			√
Fournier's gangrene (a serious infection affecting soft tissue around the groin): pain or tenderness, redness of the skin, or swelling in the genital or perineal area, with or without fever or feeling very weak, tired, or uncomfortable			√
Hemolytic anemia (breakdown of red blood cells): symptoms may include fatigue, pale colour, rapid heartbeat, shortness of breath, dark urine, chills, and backache			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Kidney problems: any change in the amount, frequency or colour (pale or dark) of urine		√	
Lactic acidosis (high levels of acid in the blood): feeling very weak, tired or uncomfortable, unusual muscle pain, trouble breathing, unusual or unexpected stomach discomfort, feeling cold, feeling dizzy or lightheaded, unusual fatigue and drowsiness, suddenly develop a slow or irregular heartbeat			√
Peripheral neuropathy (a result of damage to your peripheral nerves): signs and symptoms might include gradual onset of numbness, prickling or tingling in your feet or hands, which can spread upward into your legs and arms, sharp, jabbing, throbbing, freezing or burning pain, extreme sensitivity to touch, lack of coordination and falling, muscle weakness or paralysis if motor nerves are affected			√
VERY RARE			
Acute kidney infection: painful, urgent or frequent urination, lower back (flank) pain, fever or chills, cloudy or foul smelling urine, blood in your urine			√
Liver problems: yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, unusual tiredness		√	
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid heartbeat, nausea, vomiting, tenderness when touching the abdomen		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Urosepsis (severe infection that spreads from urinary tract throughout body): fever or low body temperature, chills, rapid breathing, rapid heartbeat, pain with urination, difficulty urinating, frequent urination			√
UNKNOWN			
Hypothyroidism (underactive/low thyroid): Weight gain, tiredness, hair loss, muscle weakness, feeling cold, dry skin, constipation, puffy face, heavier than normal or irregular menstrual periods, enlarged thyroid gland		√	
Photosensitivity (sensitivity to sunlight): itchy, red skin when exposed to sunlight.		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at 15 to 30°C.
Keep out of reach and sight of children.

If you want more information about Auro-Dapagliflozin / Metformin:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.auropharma.ca or by calling 1-855-648-6681.

This leaflet was prepared by Auro Pharma Inc.

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