

PRODUCT MONOGRAPH

PrXIGDUO®

dapagliflozin and metformin hydrochloride tablets

(as dapagliflozin propanediol monohydrate and metformin hydrochloride)

5 mg dapagliflozin/850 mg metformin HCl
5 mg dapagliflozin/1000 mg metformin HCl

ATC Code: A10BD15

Combinations of oral blood glucose lowering drugs

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TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION	3
SUMMARY PRODUCT INFORMATION.....	3
INDICATIONS AND CLINICAL USE	3
CONTRAINDICATIONS.....	4
WARNINGS AND PRECAUTIONS	5
ADVERSE REACTIONS	14
DRUG INTERACTIONS	28
DOSAGE AND ADMINISTRATION	34
OVERDOSAGE.....	35
ACTION AND CLINICAL PHARMACOLOGY	35
STORAGE AND STABILITY	41
SPECIAL HANDLING INSTRUCTIONS.....	41
DOSAGE FORMS, COMPOSITION AND PACKAGING.....	41
PART II: SCIENTIFIC INFORMATION.....	43
PHARMACEUTICAL INFORMATION	43
CLINICAL TRIALS	43
DETAILED PHARMACOLOGY	54
TOXICOLOGY.....	56
REFERENCES.....	59
PART III: CONSUMER INFORMATION.....	60

FrXIGDUO®

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(as dapagliflozin propanediol monohydrate and metformin hydrochloride)

PART I: HEALTH PROFESSIONAL INFORMATION

Note: for additional information on dapagliflozin and metformin hydrochloride, consult the individual Product Monographs.

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet / 5 mg/850 mg and 5 mg/1000 mg	<i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

INDICATIONS AND CLINICAL USE

XIGDUO (dapagliflozin/metformin hydrochloride) 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 CLINICAL TRIALS).

XIGDUO is indicated for 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 CLINICAL TRIALS).

XIGDUO is indicated for 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 CLINICAL TRIALS).

XIGDUO is indicated for 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 CLINICAL TRIALS).

Geriatrics (≥65 years of age): XIGDUO 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 (see WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Metformin is eliminated by the kidney, and the risk of serious adverse reactions to the drug is greater in patients with impaired renal function. As aging is associated with renal function, XIGDUO should be used with caution as age increases (see WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Pediatrics (<18 years of age): XIGDUO should not be used in pediatric patients. Safety and effectiveness of XIGDUO have not been established in patients under 18 years of age.

Important Limitations of Use: XIGDUO is not indicated for use in combination with pioglitazone (see WARNINGS AND PRECAUTIONS).

CONTRAINDICATIONS

- Unstable and/or insulin-dependent (Type I) diabetes mellitus.
- Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma, history of ketoacidosis with or without coma, history of lactic acidosis, irrespective of precipitating factors.
- In patients with serum creatinine levels above the upper limit of normal range or when renal function is not known, renal disease or renal dysfunction, e.g., as suggested by serum creatinine levels ≥ 136 $\mu\text{mol/L}$ (males), ≥ 124 $\mu\text{mol/L}$ (females), or abnormal creatinine clearance (< 60 mL/min), which may result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see WARNINGS AND PRECAUTIONS).
- Excessive alcohol intake, acute or chronic.
- XIGDUO (dapagliflozin/metformin hydrochloride) should not be used in patients with clinical or laboratory evidence of hepatic disease (see WARNINGS AND PRECAUTIONS, Hepatic). Severe hepatic dysfunction has been associated with cases of lactic acidosis.
- Cardiovascular collapse and in disease states associated with hypoxemia such as cardiorespiratory insufficiency, which are often associated with hyperlactacidemia.
- Stress conditions, such as severe infections, trauma or surgery and the recovery phase thereafter.
- Severe dehydration.

- Known hypersensitivity to dapagliflozin, metformin or to any ingredient in the formulation. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.
- During pregnancy and breastfeeding (see WARNINGS AND PRECAUTIONS, Special Populations).
- Period around administration of iodinated contrast materials, because the use of such products may result in acute alteration of renal function (see WARNINGS AND PRECAUTIONS, Renal).

WARNINGS AND PRECAUTIONS

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 XIGDUO (dapagliflozin/metformin hydrochloride) (see Endocrine and Metabolism, Lactic Acidosis section below).
- Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking XIGDUO, since alcohol intake potentiates the effect of metformin on lactate metabolism (see Endocrine and Metabolism, Lactic Acidosis section below).

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 cases have been atypical with blood glucose values below 13.9 mmol/L (250 mg/dL) (see ADVERSE REACTIONS). Some cases of DKA have been fatal.
- 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, XIGDUO should be **discontinued immediately**.
- XIGDUO should not be used for the treatment of DKA or in patients with a history of DKA.
- XIGDUO is not indicated, and should not be used, in patients with type 1 diabetes.

Carcinogenesis and Mutagenesis

Dapagliflozin

Bladder cancer: An imbalance in bladder cancers was observed in clinical trials however, there are insufficient data to determine whether dapagliflozin has an effect on pre-existing bladder tumors (see ADVERSE REACTIONS). Consequently, dapagliflozin should not be used in patients with active bladder cancer and should be used with caution in patients with a prior history of bladder cancer.

Use in patients treated with pioglitazone: The relationship between dapagliflozin, pioglitazone and bladder cancer is uncertain. Therefore, as a precautionary measure, dapagliflozin is not indicated for use in patients concomitantly treated with pioglitazone.

Cardiovascular

Dapagliflozin

Use in patients at risk for volume depletion, hypotension and/or electrolyte imbalances: Due to its mechanism of action, dapagliflozin causes diuresis that may be associated with decreased 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.

Patients most susceptible to adverse reactions related to reduced intravascular volume (e.g., postural dizziness, orthostatic hypotension, hypotension or renal failure) include patients with renal impairment, patients with known cardiovascular disease, patients on antihypertensive therapy (particularly on loop diuretics or medications that interfere with the renin-angiotensinaldosterone system (e.g., angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs])), elderly patients, patients with low systolic blood pressure, or in case of intercurrent conditions that may lead to volume depletion (such as gastrointestinal illness) (see ADVERSE REACTIONS, DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION).

Careful monitoring of volume status is recommended. Temporary interruption of XIGDUO should be considered for patients who develop volume depletion until the depletion is corrected (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and 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, XIGDUO should be promptly discontinued.

Endocrine and Metabolism

Dapagliflozin

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 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) (see ADVERSE REACTIONS). Some cases of DKA have been fatal.

XIGDUO is not indicated and, should not be used, in patients with type 1 diabetes. The diagnosis of T2DM should therefore be confirmed before initiating XIGDUO.

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 XIGDUO treatment and be assessed for DKA immediately.**

Interruption of treatment with XIGDUO should be considered in T2DM patients who are hospitalized for major surgical procedures, serious infections or acute serious medical illness.

Conditions that can precipitate DKA while taking XIGDUO 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 DOSAGE AND ADMINISTRATION).

Hypoglycemia

Use with medications known to cause hypoglycemia: Insulin and insulin secretagogues, such as sulfonylureas, causes hypoglycemia. Therefore, a lower dose of insulin may be required to reduce the risk of hypoglycemia when used in combination with dapagliflozin and metformin (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

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

Metformin hydrochloride

Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose 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.

The patient should be warned about driving a vehicle or operating machinery under these conditions where risk of hypoglycemia is present.

Lactic acidosis: Lactic acidosis is a rare, but serious metabolic complication that can occur due to metformin accumulation during treatment with XIGDUO; 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 $\mu\text{g/mL}$ 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 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 CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Cardiovascular, Hepatic 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, XIGDUO should be discontinued immediately.

Change in clinical status of previously controlled Type 2 diabetes patients:

A type 2 diabetic patient previously well controlled on 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, XIGDUO 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. XIGDUO may be reinstated after the acute episode is resolved.

Vitamin B₁₂ levels: In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum Vitamin B₁₂ levels, without clinical

manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B₁₂ absorption from the B₁₂-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B₁₂ supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on metformin and any apparent abnormalities should be appropriately investigated and managed (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests). Certain individuals (those with inadequate Vitamin B₁₂ or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B₁₂ levels. Measurements of serum Vitamin B₁₂ are advisable at least every one to two years in patients on long term metformin therapy.

Genitourinary

Dapagliflozin

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

Urinary tract infections (including urosepsis and pyelonephritis): Treatment with dapagliflozin increases the risk for urinary tract infections (see ADVERSE REACTIONS). There have been post-marketing reports of serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization in patients treated with dapagliflozin.

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 ADVERSE REACTIONS). XIGDUO should be used with caution in patients with an elevated hematocrit.

Hepatic/Biliary/Pancreatic

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 DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY). Use of XIGDUO is contraindicated in patients with severe hepatic impairment.

Metformin hydrochloride

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

Peri-Operative Consideration

XIGDUO therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids). XIGDUO should be discontinued 2 days before surgical intervention and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Renal

Dapagliflozin

The efficacy of dapagliflozin is dependent on renal function. Renal function should be assessed prior to initiation of dapagliflozin and regularly thereafter. Dapagliflozin increases serum creatinine and decreases of eGFR in a dose dependent fashion. Renal function abnormalities can occur after initiating dapagliflozin. Post-marketing cases of acute kidney injury, including acute renal failure, shortly after the initiation of dapagliflozin treatment have been reported (see WARNINGS AND PRECAUTIONS, Cardiovascular and ADVERSE REACTIONS). Patients with hypovolemia may be more susceptible to these changes (see ADVERSE REACTIONS). XIGDUO should be discontinued when serum creatinine level is above the upper limit of normal range (see CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

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. Thus, patients with serum creatinine levels above the upper limit of the normal range for their age should not receive XIGDUO. Before initiation of XIGDUO therapy and every 6 months while on XIGDUO therapy, renal function should be assessed and verified as being within normal range.

In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and XIGDUO discontinued if evidence of renal impairment is present.

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 (see DRUG INTERACTIONS), should be used with caution.

Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials): Intravascular contrast studies

with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see CONTRAINDICATIONS). Therefore, in patients in whom any such study is planned, XIGDUO should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstated only after renal function has been re-evaluated and found to be normal.

Special Populations

Pregnant Women: XIGDUO is contraindicated in pregnancy (see CONTRAINDICATIONS). There are no adequate and well-controlled studies in pregnant women with XIGDUO or their individual components; therefore, the safety of XIGDUO in pregnant women is not known. When pregnancy is detected, XIGDUO 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 TOXICOLOGY).

Metformin hydrochloride

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 CONTRAINDICATIONS).

Nursing Women: XIGDUO is contraindicated in nursing (see CONTRAINDICATIONS). No studies in lactating animals have been conducted with XIGDUO.

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 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.

Pediatrics (<18 years of age): Safety and effectiveness of XIGDUO in pediatric patients have not been established. Therefore, XIGDUO should not be used in this patient population.

Geriatrics (≥65 years of age): Metformin is eliminated by the kidney, XIGDUO should be used with caution as age increases because elderly patients are more likely to have decreased renal function (see WARNINGS AND PRECAUTIONS, Renal and DOSAGE AND ADMINISTRATION, Geriatrics).

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. After controlling for renal function (eGFR), there was no conclusive evidence suggesting that age is an independent factor affecting efficacy. 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.

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, metformin should only be used in patients with normal renal function (see CONTRAINDICATIONS). Because aging is associated with reduced renal function, metformin should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function.

Monitoring and Laboratory Tests

Blood glucose and HbA1c: Response to XIGDUO 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 DRUG INTERACTIONS, Drug-Laboratory Interactions).

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 B₁₂ deficiency should be excluded.

Renal function: XIGDUO is contraindicated in patients with a serum creatinine level above the upper limit of normal range or when renal function is not known (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION). Renal function should be assessed prior to initiation of dapagliflozin and regularly thereafter.

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

Reduced intravascular volume: XIGDUO is not recommended for use in patients who are volume depleted (see DOSAGE AND ADMINISTRATION). Before initiating XIGDUO, assess volume status, particularly in patients at risk (see WARNINGS AND PRECAUTIONS, Cardiovascular, and DOSAGE AND ADMINISTRATION) as well as in case of intercurrent conditions that may lead to fluid loss (such as a gastrointestinal illness) for patients already taking dapagliflozin. 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. Temporary interruption of treatment with XIGDUO 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 XIGDUO due to dose-dependent increases in LDL-C seen with dapagliflozin therapy.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

There have been no clinical studies conducted with XIGDUO (dapagliflozin/metformin hydrochloride) tablets. XIGDUO 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 ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Dapagliflozin and Metformin hydrochloride

The overall incidence of adverse events in a pool of patients from 8-study, short-term, placebo-controlled studies of dapagliflozin coadministered 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 ($\geq 5\%$) 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 ($\geq 5\%$) 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%).

Metformin hydrochloride

Lactic acidosis: very rare ($<1/10,000$ and isolated reports) (see WARNINGS AND PRECAUTIONS, and 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 ($\geq 1/100$): 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 B₁₂ levels; serum folic acid levels did not decrease significantly (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism). Five cases of megaloblastic anemia have been reported with metformin administration and no increased incidence of neuropathy has been observed.

Decrease of Vitamin B₁₂ absorption with decrease of serum levels during long-term use of metformin is rare ($\geq 1/10,000$ and $< 1/1,000$). 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.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Dapagliflozin and Metformin hydrochloride

Data from a prespecified pool of 8 short-term, placebo-controlled studies of dapagliflozin coadministered 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 1 shows common adverse reactions associated with the use of dapagliflozin and metformin.

Table 1 Adverse Events (Regardless of Investigator Assessment of Causality) Reported in $\geq 2\%$ 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		
	Dapagliflozin 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

Table 1 Adverse Events (Regardless of Investigator Assessment of Causality) Reported in $\geq 2\%$ 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
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.

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).

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

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

	% of Patients (Pool of 12 Placebo-controlled Studies)
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System organ class Preferred term	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, 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 $\geq 5\%$ 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 3 Adverse Events Reported in $\geq 5\%$ 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)

Less Common Clinical Trial Adverse Drug Reactions (<2 %)¹

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

Description of Selected Adverse Reactions

Volume depletion and hypotension: Events related to volume depletion (including reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension) were reported in 0.6%,

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.

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 $\leq 0.2\%$ of patients across the 21 active- and placebo-controlled studies and were balanced between dapagliflozin 10 mg and comparator. In subgroup analyses of patients on loop diuretics or ≥ 65 years of age in the 13-study placebo-controlled pool, the proportions of patients with events related to volume depletion were higher in patients treated with dapagliflozin 10 mg than in those treated with placebo (events in patients on loop diuretics: 2.5% vs. 1.5%; events in patients ≥ 65 years of age: 1.7% vs. 0.8%, respectively).

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 2).

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 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 4). Studies of dapagliflozin as an add-on to insulin therapy had higher rates of hypoglycemia with dapagliflozin treatment than with placebo treatment (see WARNINGS AND PRECAUTIONS).

Table 4 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 Sulfonyleurea (24 weeks)	-	N = 109	N = 109
Major [n (%)]	-	0	0
Minor [n (%)]	-	14 (12.8)	4 (3.7)
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)

* Major episodes of hypoglycemia were defined as symptomatic episodes requiring external (third party) assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value <3 mmol/L and prompt recovery after glucose or glucagons 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.

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 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.

Bladder cancer: Across 22 clinical studies, newly diagnosed cases of bladder cancer were reported in 10/6045 patients (0.17%) treated with dapagliflozin and 1/3512 patient (0.03%) treated with placebo/comparator. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 4 cases with dapagliflozin and no cases with placebo/comparator. Bladder cancer risk factors (e.g. smoking, age) and hematuria (a potential indicator of pre-existing tumors) were balanced between treatment arms at baseline. There were too few cases to determine whether the emergence of these events is related to dapagliflozin.

Cardiovascular safety: A meta-analysis of cardiovascular events across placebo-controlled studies with dapagliflozin was performed. The number of subjects per treatment was 4016 for dapagliflozin 5/10 mg and 2776 for placebo. Cardiovascular events were adjudicated by an independent adjudication committee. The primary endpoint was the time to first event of the following outcomes: cardiovascular death, stroke, myocardial infarction, and hospitalization

for unstable angina. Primary events occurred at a rate of 1.86% per 100 patient-years in patients treated with dapagliflozin 5/10 mg/day and 2.41% in placebo-treated patients, per 100 patient-years. The hazard ratio comparing dapagliflozin to placebo was 0.77 (95% confidence interval; 0.55, 1.07). Therefore, there was no evidence of an increase in the primary endpoint with dapagliflozin 5 mg/10 mg relative to placebo.

Patients with renal impairment: Safety was assessed in a dedicated study of diabetic patients with moderate renal impairment (eGFR 30 to 60 mL/min/1.73m²). At Week 52, dapagliflozin was associated with changes from baseline in mean eGFR (eGFR: dapagliflozin 5 mg: -2.08 mL/min/1.73m², dapagliflozin 10 mg -4.46 mL/min/1.73m² and placebo -2.58 mL/min/1.73m²). At Week 104, these changes persisted (eGFR: dapagliflozin 5 mg -1.71 mL/min/1.73m², dapagliflozin 10 mg -3.50 mL/min/1.73m² and placebo -2.38 mL/min/1.73 m²). 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. At Week 52 and persisting through Week 104, greater increases in mean PTH and serum phosphorus were observed in this study with dapagliflozin 5 mg and 10 mg compared to placebo, where baseline values of these analytes were higher.

Overall, there were 13 patients with an adverse event of bone fracture reported in this study up to Week 104 of which 8 occurred in the dapagliflozin 10 mg group, 5 occurred in the dapagliflozin 5 mg group, and none occurred in the placebo group. Eight (8) of these 13 fractures were in patients who had eGFR 30 to 45 mL/min/1.73m² and 11 of the 13 fractures were reported within the first 52 weeks.

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. XIGDUO 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 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism).

Abnormal Hematologic and Clinical Chemistry 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 5 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/1.73m²				
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 6 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 7 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, $\mu\text{mol/L}$ (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 \geq 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 8 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

Study Week/ Treatment Group	Week 24*		Week 102**	
	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo
Mean Percent Changes from Baseline				
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 B₁₂ levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B₁₂ absorption from the B₁₂-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B₁₂ supplementation (see WARNINGS AND PRECAUTIONS).

Post-Market Adverse Drug 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

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

Investigations: blood lactic acid increased

Metabolism and nutrition disorders: lactic acidosis, decrease of Vitamin B₁₂ absorption with decrease of serum levels during long-term use of metformin, weight decreased, decreased appetite

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

Dapagliflozin

Genitourinary: severe urinary tract infections; urosepsis and pyelonephritis

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)

DRUG INTERACTIONS

Overview

Specific pharmacokinetic drug interactions studies with XIGDUO 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 coadministered 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.

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 coadministered drugs (see Table 9).

Table 9 Effects of Coadministered Drugs on Dapagliflozin Systemic Exposure

Coadministered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Effect on Dapagliflozin Exposure Ratio of Adjusted Geometric Means (90% CI)		Clinical Comment
		C _{max}	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)	NA ^{††}
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				

Coadministered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Effect on Dapagliflozin Exposure Ratio of Adjusted Geometric Means (90% CI)		Clinical Comment
		C _{max}	AUC [†]	
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 coadministration (45 g).

^{††} Pioglitazone is not indicated for coadministration with dapagliflozin.

Effect of dapagliflozin on other drugs

In studies conducted in healthy subjects, as described below, dapagliflozin did not alter the pharmacokinetics of the coadministered drugs (see Table 10).

Table 10 Effects of Dapagliflozin on the Systemic Exposures of Coadministered Drugs

Coadministered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Effect on Coadministered 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)	NA ^{††}
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

Table 10 Effects of Dapagliflozin on the Systemic Exposures of Coadministered Drugs

Coadministered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Effect on Coadministered Drug Exposure Ratio of Adjusted Geometric Means (90% CI)		Clinical Comment
		C _{max}	AUC [†]	
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
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
Warfarin (25 mg)***	20 mg loading dose then 10 mg once daily for 7 days	S-warfarin		No dosing adjustment required
		1.030 (0.994, 1.124)	1.068 (1.002, 1.138)	
		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.

** Coadministration 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]).

†† Pioglitazone is not indicated for coadministration with dapagliflozin.

Diuretics: Dapagliflozin may add to the diuretic effect of loop diuretics and may increase the risk of dehydration and hypotension. Caution is recommended when XIGDUO is co-administered with diuretics, particularly loop diuretics (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Metformin hydrochloride

Glyburide: In a single-dose interaction study in type 2 diabetes patients, coadministration 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 coadministration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when coadministered chronically.

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

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 XIGDUO therapy, with an increased risk of hemorrhage.

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.

Drug-Food Interactions

Interactions with food have not been studied (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory 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 1,5AG 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 CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Drug-Lifestyle 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 XIGDUO, since alcohol intake potentiates the effect of metformin on lactate metabolism (see CONTRAINDICATIONS). The risk of lactic acidosis is increased in acute alcohol intoxication, particularly in case of fasting or malnutrition or hepatic insufficiency. XIGDUO is contraindicated in patients with clinical or laboratory evidence of hepatic disease (see CONTRAINDICATIONS). It is recommended that consumption of alcohol and alcohol-containing medicinal product be avoided.

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 XIGDUO is used as add-on therapy with insulin.

DOSAGE AND ADMINISTRATION

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 may be necessary to reduce the risk of hypoglycemia (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).

Diuretics: Dapagliflozin should be used with caution in patients taking diuretics, particularly loop diuretics, due to the increased risk of adverse events due to volume depletion during coadministration.

Recommended Dose and Dosage Adjustment

The recommended dose of XIGDUO 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 XIGDUO 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 following dosage strengths are available:

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

Pediatrics (<18 years of age): Safety and effectiveness of XIGDUO in pediatric patients have not been established. Therefore, XIGDUO should not be used in this patient population.

Geriatric (≥65 years of age): XIGDUO should be used with caution as age increases because metformin is eliminated in part by the kidney, and elderly patients are more likely have decreased renal function associated with aging and the risk of developing lactic acidosis (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

Renal impairment: The efficacy of XIGDUO is dependent on renal function. Assessment of renal function is recommended prior to initiation of XIGDUO therapy and periodically thereafter. XIGDUO should be discontinued when serum creatinine level is above the upper limit of normal range (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Hepatic impairment: XIGDUO is not recommended in patients with clinical or laboratory evidence of hepatic disease (see CONTRAINDICATIONS). Dapagliflozin exposure is increased in patients with severe hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics). Metformin use in patients with impaired hepatic function has been associated with some cases of lactic acidosis (see WARNINGS AND PRECAUTIONS).

Missed Dose

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

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 overdose 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 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Lactic Acidosis). 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 overdose is suspected.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Dapagliflozin and metformin hydrochloride

XIGDUO combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes: 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 type 2 diabetes mellitus by reducing renal glucose reabsorption leading to urinary excretion of excess glucose (glucuresis).

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.

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.

Pharmacodynamics

Dapagliflozin

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following the administration of dapagliflozin. Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day) at a dapagliflozin dose of 10 mg/day in patients with type 2 diabetes mellitus for 12 weeks. This glucose elimination rate approached the maximum glucose excretion observed at 20 mg/day of dapagliflozin. Evidence of sustained glucose excretion was seen in patients with type 2 diabetes mellitus given dapagliflozin 10 mg/day for up to 2 years.

This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume 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 $\mu\text{mol/L}$ (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).

Pharmacokinetics

XIGDUO 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 XIGDUO 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 [14 C]-dapagliflozin dose and was the predominant drug-related component in human plasma, accounting for 42% (based on $AUC_{[0-12\text{ h}]}$) 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 WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Excretion:

Dapagliflozin

Dapagliflozin and related metabolites are primarily eliminated via urinary excretion, of which less than 2% is unchanged dapagliflozin. After administration of 50 mg [14 C]-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

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

XIGDUO is contraindicated in this patient population. No studies were conducted in the pediatric population.

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.

Gender:

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).

Race:

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.

Body weight: *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 type 2 diabetes mellitus patients with high body weight (≥ 120 kg) is recommended.

Subjects with low body weights (<50 kg) were not well represented in the healthy subject and patient studies used in the population pharmacokinetic analysis. Therefore, 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 type 2 diabetes mellitus patients with low body weight (<50 kg) is recommended.

Renal impairment:

XIGDUO is contraindicated in patients serum creatinine levels above the upper limit of normal range or when renal function is not known (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS and 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 type 2 diabetes 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 type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. There were no differences in the protein binding of dapagliflozin between renal impairment groups or compared to healthy subjects. The impact of hemodialysis on dapagliflozin exposure is not known.

Hepatic impairment:

XIGDUO is contraindicated in patients with clinical or laboratory evidence of hepatic disease (see 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.

STORAGE AND STABILITY

Store at room temperature (15-30°C).

SPECIAL HANDLING INSTRUCTIONS

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Packaging

XIGDUO (dapagliflozin/metformin hydrochloride) is available for oral administration as immediate release tablets containing dapagliflozin as dapagliflozin propanediol monohydrate and metformin hydrochloride in the following formats:

XIGDUO (dapagliflozin/metformin hydrochloride) 5 mg/850 mg tablets are brown, oval, biconvex, film coated tablets. The tablets are debossed “5/850” on one side and “1067” on the other side.

XIGDUO (dapagliflozin/metformin hydrochloride) 5 mg/1000 mg tablets are yellow, oval, biconvex, film coated tablets. The tablets are debossed “5/1000” on one side and “1069” on the other side.

XIGDUO tablets are provided in 10-count blisters in cartons of 60 for both strengths.

Information for the patient is provided as a consumer information leaflet within the XIGDUO packages.

Composition

XIGDUO is available as a film-coated tablet for oral administration containing the equivalent of 5 mg dapagliflozin as dapagliflozin propanediol monohydrate and 850 mg or 1000 mg metformin hydrochloride.

Each film-coated tablet of XIGDUO also contains the following inactive ingredients: cellulose microcrystalline, hydroxypropylcellulose, magnesium stearate (extragranular), sodium starch glycolate.

The 5 mg/850 mg film coating contains the following inactive ingredients: polyvinyl alcohol, macrogol/polyethylene glycol 3350, talc, titanium dioxide, iron oxide yellow and iron oxide red.

The 5 mg/1000 mg film coating contains the following inactive ingredients: polyvinyl alcohol, macrogol/polyethylene glycol 3350, talc, titanium dioxide and iron oxide yellow.

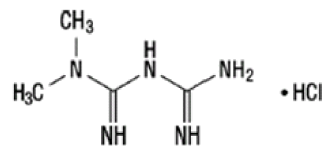
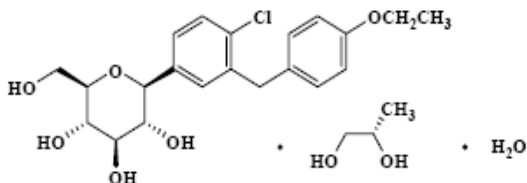
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common Name:	dapagliflozin propanediol monohydrate	Metformin hydrochloride
Chemical Name:	D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1 <i>S</i>)-,compd. with (2 <i>S</i>)-1,2-propanediol, hydrate (1:1:1)	N,N-dimethyl biguanide hydrochloride or N,N-dimethylimidodicarbonimidic diamide hydrochloride
Molecular Formula and Molecular Mass:	$C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$ 502.98; 408.87 (dapagliflozin)	$C_4H_{11}N_5 \cdot HCl$ 165.63

Structural Formula:



Physicochemical Properties:	Dapagliflozin propanediol is a white to off-white non-hygroscopic crystalline powder. It is slightly soluble in water, soluble in acetonitrile and freely soluble in acetone, ethanol, isopropanol, methanol and tetrahydrofuran.	Metformin hydrochloride is a white to off-white crystalline compound. It is soluble in water and in 95% ethyl alcohol. It is practically insoluble in ether and in chloroform.
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CLINICAL TRIALS

There have been no clinical studies conducted with XIGDUO (dapagliflozin/metformin hydrochloride) tablets. XIGDUO 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 ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

The coadministration 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 11).

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 BMI. In addition, patients treated with dapagliflozin compared to placebo or control achieved greater HbA1c reductions in patients with a baseline HbA1c \geq 9%.

Study demographics and trial design

Table 11 Summary of patient demographics for clinical trials in specific indication

Trial design	Dosage, route of administration and duration	N per group/ N treated with dapagliflozin/ Total	Mean age	Gender (% M/F)
Add-on Combination Therapy with Metformin				
Multicentre, randomized, double-blind, placebo-controlled ¹	4 groups: dapagliflozin 2.5, 5, or 10 mg or placebo Background therapy: metformin \geq 1500 mg/day Oral, 24 weeks + 78 weeks	135 - 137/ 409/ 546 (ST)	53.9	53/47
Multicentre, randomized, double-blind, active-controlled ⁷	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 \geq 1500 mg Oral, 52 weeks + 52 weeks + 52 weeks	406 - 408/ 406/ 814 (ST)	58.4	55/45
Multicentre, randomized, double-blind, placebo-controlled ⁸	4 groups: dapagliflozin 2.5 mg BID, 5 mg BID, 10 mg QD or placebo Background therapy: metformin \geq 1500 mg/day Oral, 16 weeks	99-101/ 298 399	57.7	45/55
Add-on Combination Therapy with Metformin and a Sulfonylurea				

Trial design	Dosage, route of administration and duration	N per group/ N treated with dapagliflozin/ Total	Mean age	Gender (% M/F)
Multicentre, randomized, double-blind, placebo-controlled	2 groups: dapagliflozin 10 mg or placebo Background therapy: metformin \geq 1500 mg and a sulfonylurea (at maximum tolerated dose and \geq 50% of maximum recommended dose) Oral, 24 weeks + 28 weeks	109/ 109/ 218 (ST)	61.0	49/51
Add-on Combination Therapy with Sitagliptin with Metformin				
Multicentre, randomized, double-blind, placebo-controlled ⁶	2 groups: dapagliflozin 10 mg or placebo Background therapy: Sitagliptin 100 mg/day (+/- metformin \geq 1500 mg) Oral, 24 weeks + 24 weeks	225 – 226/ 225/ 451 (ST)	55.0	55/45
Add-on Combination Therapy with Insulin				
Multicentre, randomized, double-blind, placebo-controlled ¹⁰	4 groups: dapagliflozin 2.5, 5, or 10 mg or placebo Background therapy: insulin \geq 30 IU/day \pm 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

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 \geq 7% and \leq 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 12, 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 \geq 6.5% and \leq 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 12.

Table 12 Results of Placebo-Controlled Studies of Dapagliflozin in Add-On Combination with Metformin up to 24 weeks

Efficacy Parameter	Study D1691C00003 (16-week study)		Study MB102014 (24-week study)	
	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 analysed 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 13, 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 13 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 [‡]) (95% CI)	0.00 [¶] (-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 [‡]) (95% CI)	-4.65 [§] (-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

Patients with type 2 diabetes and inadequate glycemic control (HbA1c $\geq 7\%$ and $\leq 10.5\%$) 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.

As shown in Table 14, 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 14 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 ^{‡, §§}) (95% CI)	-0.69 [§] (-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 [‡]) (95% CI)	-1.86 [§] (-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 [‡]) (95% CI)	-2.07 [§] (-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

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 $\geq 7.0\%$ and $\leq 10.0\%$ 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.

As shown in Table 15, 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 15 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 [‡]) (95% CI)	-0.40 [§] (-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 [‡]) (95% CI)	-1.62 [§] (-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

Table 15 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 [†]
Difference from placebo (adjusted mean [‡]) (95% CI)	-1.87 [§] (-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

Patients with type 2 diabetes who had inadequate glycemic control (HbA1c $\geq 7.5\%$ and $\leq 10.5\%$) 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 16); the effect of dapagliflozin on HbA1c was similar in patients in both strata.

Table 16 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 [‡]) (95% CI)	-0.60 [§] (-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 [‡]) (95% CI)	-1.4 [§] (-1.9, -0.9)	
Body Weight (kg)		
Baseline mean	94.63	94.21
Change from baseline (adjusted mean [‡])	-1.67	0.02
Difference from placebo (adjusted mean [‡]) (95% CI)	-1.68 [§] (-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.

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

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 $\geq 7.0\%$ and $\leq 10.0\%$), 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 cardiovascular 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.

For both studies, at Week 24 treatment with dapagliflozin 10 mg provided significant improvement in HbA1c compared with placebo (Table 17). 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 17 Results at Week 24 (LOCF^{*}) in Two Placebo-Controlled Studies Comparing Dapagliflozin to Placebo in Patients with Type 2 Diabetes and Cardiovascular Disease

Efficacy Parameter	Study D1690C00018		Study D1690C00019	
	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 Patients²

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 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 18).

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 18 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 [‡]) (95% CI)	-2.08 ^β (-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 [‡]) (95% CI)	-2.76 [§] (-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 [‡]) (95% CI)	-1.22 [§] (-2.36, -0.08)	
Body Fat Mass (kg)		

Table 18 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[†]
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 [‡]) (95% CI)	-1.48 ^β (-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.

DETAILED PHARMACOLOGY

Dapagliflozin

The sodium-glucose cotransporter 2 (SGLT2) is selectively expressed in the kidney³ and is responsible for the majority of reabsorption of filtered glucose at that site. Dapagliflozin *in vitro* is a potent, competitive and reversible inhibitor of SGLT2. 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 absorption is relatively slow and may extend over about 6 hours. Animal studies with metformin, labelled with ¹⁴C have shown that the drug is neither concentrated by liver cells nor is it excreted in the bile; it is concentrated in the intestinal mucosa and salivary glands.

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.

Metformin is eliminated in feces and urine. It is rapidly excreted by the kidneys in an unchanged form.

Renal clearance is 450 mL/minute; this appears to explain the absence of accumulation.

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

A single Rf spot is always present following radiochromatographic 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.

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 \times the human exposures (AUC) at the maximum recommended human dose (MRHD) of 10 mg/day resulting in AUC 0.465 $\mu\text{g}\cdot\text{h}/\text{mL}$, and in dogs for up to 12 months at doses of ≤ 120 mg/kg/day (up to 3300 \times 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 ($\geq 2100\times$ the MRHD). Despite achieving exposure multiples of $\geq 3200\times$ 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.

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.

Mutagenesis

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 $\mu\text{g/mL}$. Dapagliflozin was negative for clastogenicity *in vivo* in a series of studies evaluating micronuclei or DNA repair in rats at exposure multiples $>2100\times$ 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.

Reproduction

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.

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.

Development

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 $\geq 15\times$ the MRHD. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1-month recovery period.

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 $1415\times$ and $137\times$, 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 $\geq 29\times$ 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 $19\times$ 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 ($184\times$ the MRHD). In rats, dapagliflozin was not teratogenic at doses up to 75 mg/kg/day ($1441\times$ the MRHD). Doses ≥ 150 mg/kg/day ($\geq 2344\times$ 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 centra, and duplicated manubria and sternal centra. Variations were primarily reduced ossifications.

Metformin hydrochloride

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the 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.

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**PART III:
CONSUMER INFORMATION**

Pr XIGDUO®

**dapagliflozin and metformin hydrochloride tablets
(as dapagliflozin propanediol monohydrate and
metformin hydrochloride)**

Read this carefully before you start taking XIGDUO 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 XIGDUO.

ABOUT THIS MEDICATION

What the medication is used for:

XIGDUO is used along with diet and exercise in adults with type 2 diabetes to help control their blood sugar levels. XIGDUO can be used:

- in patients taking dapagliflozin (FORXIGA®) and metformin as separate tablets, or
- in patients taking dapagliflozin (FORXIGA®), metformin and a sulfonyleurea as separate tablets, or
- in patients taking dapagliflozin (FORXIGA®), metformin and sitagliptin as separate tablets, or
- in patients taking dapagliflozin (FORXIGA®), metformin and insulin.

What it does:

XIGDUO 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.

When it should not be used:

Do not take XIGDUO if you:

- have unstable and/or insulin-dependent (Type I) diabetes mellitus.
- have increased ketones in the blood or urine (metabolic acidosis) or have had ketoacidosis with or without coma.
- have diabetic ketoacidosis (DKA, a complication of diabetes) or a history of DKA.

- have a history of too much acid in the blood (lactic acidosis).
- have or ever had kidney or liver problems.
- consume large amounts of alcohol all the time or short-term ‘binge’.
- have heart failure or other severe heart problems.
- are stressed, have a serious infection, have recently had a trauma, are about to have surgery or are recovering from surgery.
- are dehydrated (have lost a lot of water from your body).
- are allergic (hypersensitive) to dapagliflozin, metformin hydrochloride or any of the ingredients listed below.
- have bladder cancer.
- take pioglitazone, a drug to reduce the amount of sugar in the blood.
- are pregnant or planning to become pregnant; it is not known if XIGDUO will harm your unborn baby. Talk with your doctor about the best way to control your blood sugar while you are pregnant.
- are breast-feeding or plan to breast-feed; it is not known if XIGDUO will pass into your breast milk. Talk to your doctor if you would like to breast feed.
- will have certain x-ray tests with injectable dyes or contrast agents. Talk to your physician or pharmacist about when to stop XIGDUO and when to start again.

What the medicinal ingredients are:

XIGDUO contains dapagliflozin (as dapagliflozin propanediol monohydrate) and metformin hydrochloride.

What the nonmedicinal ingredients are:

cellulose microcrystalline, hydroxypropylcellulose, magnesium stearate (extragranular) and sodium starch glycolate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, macrogol/polyethylene glycol, talc, titanium dioxide, yellow iron oxide and/or red iron oxide.

What dosage forms it comes in:

XIGDUO is supplied as tablets containing dapagliflozin/metformin hydrochloride 5 mg/850 mg or 5 mg/1000 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- XIGDUO contains metformin and it can rarely cause a serious condition that can cause death called lactic acidosis. Alcohol may increase the risk of lactic acidosis. Do not drink a lot of alcohol while taking XIGDUO (see Lactic Acidosis section below).
- Diabetic ketoacidosis (DKA) is a serious and life-threatening condition that requires urgent hospitalization. DKA has been reported in patients with type 2 diabetes mellitus (T2DM) with normal or high blood sugar levels, who are treated with dapagliflozin and other sodium-glucose co-transporter 2 (SGLT2)

inhibitors. Some cases of DKA have led to death.

- Seek medical attention right away and **stop taking XIGDUO immediately** 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 XIGDUO if you have:
 - DKA or a history of DKA
 - type 1 diabetes

Lactic Acidosis

Stop taking XIGDUO and tell your doctor if you get the following symptoms of lactic acidosis:

- You feel very weak and tired.
- You have unusual (not normal) muscle pain.
- You have trouble breathing or fast breathing.
- You have stomach pain with nausea and vomiting, or diarrhea.
- You feel cold, especially in your arms and legs.
- You feel dizzy or lightheaded.
- You feel unusual fatigue and drowsiness.
- You have a slow or irregular heart beat.
- Your medical condition suddenly changes.
- You develop or experience a worsening of heart problems and particularly heart failure.

BEFORE you use XIGDUO talk to your doctor or pharmacist if you:

- have type 1 diabetes (your body does not produce any insulin). XIGDUO should not be used in patients with type 1 diabetes.
- have an increased chance of developing DKA, including if you:
 - are dehydrated or suffer from excessive vomiting, diarrhea, or sweating;
 - are on a very low carbohydrate diet;
 - drink a lot of alcohol;
 - have/have had problems with your pancreas, including pancreatitis or surgery on your pancreas;
 - are hospitalized for major surgery, serious infection or serious medical illnesses;
 - have a history of diabetic ketoacidosis (DKA).
- are older than 65 years of age.
- have heart problems or low blood pressure.
- are taking medicines for high blood pressure or taking a water pill (used to remove excess water from the body).
- are taking medicines to lower blood sugar such as glyburide, gliclazide or glimepiride (sulfonylureas) or insulin. Taking XIGDUO with any of these

medications can increase the risk of having low blood sugar (hypoglycemia).

- have a problem with your adrenal glands (found on top of your kidneys) or pituitary gland (found in your brain).
- have a history of bladder cancer.
- will be having surgery.
- have had a heart attack, severe infection, or stroke.
- feel very weak and tired.
- are 80 years of age or older and have not had your kidney function tested.
- have low B₁₂ levels.
- have had an allergic reaction to SGLT2 inhibitors (used to treat Type 2 diabetes).
- often get urinary tract infections.

XIGDUO is not recommended for use in patients under 18 years of age.

XIGDUO will cause your urine to test positive for sugar (glucose).

XIGDUO may cause changes in the amount of cholesterol or fats in your blood.

XIGDUO increases the chance of getting a yeast infection of the penis or vagina. This is more likely in people who have had yeast infections in the past.

XIGDUO may cause abnormal kidney function. Your doctor will do blood tests to monitor how well your kidneys are working while you are taking XIGDUO.

Driving and using machines: XIGDUO may cause dizziness or lightheadedness. Do not drive or use machines until you know how the medicine affects you.

INTERACTIONS WITH THIS MEDICATION

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

Some drugs may interact with XIGDUO. Tell your doctor if you are taking:

- Medicines for diabetes; low blood sugar (hypoglycemia) may occur if you already take another medication to treat diabetes.
- Nifedipine (used to treat high blood pressure and chest pain).
- Cationic drugs (e.g. amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim and vancomycin).
- Certain “blood thinners” (phenprocoumon or other Vitamin K anticoagulants).
- Diuretics (water pills), especially loop diuretics, that may increase the risk of lactic acidosis (e.g. furosemide).

- Other drugs that tend to produce high blood sugar (hyperglycemia) and may lead to a loss of blood sugar control. Some example of drugs that can increase the blood sugar include:
 - Thiazide and other diuretics (water pills)
 - Corticosteroids (used to treat joint pain and swelling)
 - Phenothiazines (used to treat schizophrenia)
 - Thyroid products
 - Estrogens or estrogens plus progestogen
 - Oral contraceptives (birth control pills)
 - Phenytoin (used to treat epilepsy)
 - Nicotinic Acid
 - Sympathomimetics (used for heart problems)
 - Calcium channel blocking drugs (used for high blood pressure)
 - Isoniazid (used to treat tuberculosis)
 - Beta-2-agonists (used to treat breathing problems)
- ACE inhibitor drugs (may lower blood glucose).

- headache
- rash

If any of these affects you severely, tell your doctor or pharmacist.

XIGDUO can cause abnormal blood test results. Your doctor will decide when to perform blood tests. They may check how well your kidneys are working, blood fat levels (cholesterol) and the amount of red blood cells in your blood (hematocrit).

Diabetic Ketoacidosis (DKA) is a serious medical condition normally seen at high blood sugar levels; however it has also been seen at near normal blood sugar levels. Get medical help right away if you have any of the symptoms under DKA in the table below, even if your blood sugar levels are normal.

PROPER USE OF THIS MEDICATION

Follow the directions given to you by your doctor. Your doctor will tell you how many XIGDUO tablets to take and how often you need to take them.

USUAL ADULT DOSE:

The recommended adult dose is one tablet (5 mg/850 mg or 5 mg/1000 mg), twice daily, taken with a meal.

OVERDOSE:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

MISSED DOSE:

If you miss a dose of XIGDUO, wait for the next dose at the usual time. Do not take a double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

These are not all the possible side effects you may feel when taking XIGDUO. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

Side effects may include:

- sore throat
- the flu
- constipation
- diarrhea
- nausea
- back pain
- pain in the arms, legs, hands or feet

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
	Frequency / Symptom / Effect	Talk with your doctor or pharmacist		Get immediate medical help
		Only if severe	In all cases	
Common	Urinary tract infection: pain, difficulty or increased need to urinate		X	
	Yeast infection of vagina: severe itching, burning, soreness, irritation, and a whitish or whitish-gray cottage cheese-like discharge	X		
	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	X		
Uncommon	Volume depletion (loss of needed fluids from the body; dehydration): dry or sticky mouth, headache, dizziness or urinating less often than normal		X	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Frequency / Symptom / Effect		Talk with your doctor or pharmacist		Get immediate medical help
		Only if severe	In all cases	
Uncommon	Low blood pressure: dizziness, fainting, lightheadedness; may occur when you go from lying to sitting to standing up		X	
	Low blood sugar (hypoglycemia): shaking, sweating, rapid heartbeat, change in vision, hunger, headache and change in mood		X	
Rare	Lactic acidosis: Symptoms include <ul style="list-style-type: none"> • 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 			X

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Frequency / Symptom / Effect		Talk with your doctor or pharmacist		Get immediate medical help
		Only if severe	In all cases	
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.			X
	Kidney problems: any change in the amount, frequency or colour (pale or dark) of urine		X	
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			X
	Severe infection that spreads from urinary tract throughout body (sepsis): fever or low body temperature, chills, rapid breathing, rapid heartbeat, pain with urination, difficulty urinating, frequent urination			X

This is not a complete list of side effects. For any unexpected effects while taking XIGDUO, contact your doctor or pharmacist.

REPORTING SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>).

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.

HOW TO STORE IT

Store at room temperature (15-30°C).

Keep XIGDUO well out of sight and reach of children.

MORE INFORMATION

NOTE: This INFORMATION FOR THE CONSUMER leaflet provides you with the most current information at the time of printing.

The most current information, the Consumer Information Leaflet plus the full Product Monograph, prepared for health professionals can be found at: <http://www.astrazeneca.ca> or by contacting the sponsor, AstraZeneca Canada Inc. at: Customer Inquiries 1-800-668-6000, Renseignements 1-800-461-3787.

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