SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

XIGDUO 10 MG + 1000 MG PROLONGED-RELEASE TABLET

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains Dapagliflozin Propanediol equivalent to

Dapagliflozin 10 mg and Metformin. hydrochloride USP (extended release).....1000 mg

Excipient(s) with known effect:

Tablet contains less than 1 mmol sodium (23 mg) per dose, i.e., is essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Extended Release Tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

XIGDUO tablet is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Dapagliflozin is indicated to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD) or multiple cardiovascular (CV) risk factors.

4.2. Posology and method of administration

Prior to initiation of Dapagliflozin/Metformin hydrochloride tablet

• Assess renal function before initiating Dapagliflozin/Metformin hydrochloride therapy and periodically thereafter (see section 4.4)

• In patients with volume depletion, correct this condition prior to initiation of Dapagliflozin/ Metformin hydrochloride (see sections 4.4 and 5.1)

Posology Recommended dosage

- Take Dapagliflozin/Metformin hydrochloride tablet once daily in the morning with food.
- Swallow Dapagliflozin/Metformin hydrochloride tablets whole and never crush, cut, or chew. Occasionally, the inactive ingredients of Dapagliflozin/Metformin hydrochloride tablet will be eliminated in the feces as a soft, hydrated mass that may resemble the original tablet.

• Individualize the starting dose of Dapagliflozin/Metformin hydrochloride tablet based upon the patient's current regimen.

• To improve glycemic control for patients not already taking dapagliflozin, the recommended starting dose for dapagliflozin is 5 mg once daily.

• To reduce the risk of hospitalization for heart failure, the recommended dose for dapagliflozin is 10 mg once daily.

• For patients requiring a dose of 5 mg dapagliflozin and 2000 mg metformin HCl extended-release, use two of the 2.5 mg dapagliflozin/1000 mg metformin HCl extended-release tablets.

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

• Patients taking an evening dose of metformin XR should skip their last dose before starting Dapagliflozin/Metformin hydrochloride tablet.

Special populations

Renal impairment

Dapagliflozin/Metformin hydrochloride is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 mL/min/1.73 m2 (see sections

4.3, 4.4 and 5.1)

No dose adjustment for Dapagliflozin/Metformin hydrochloride is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m2.

Dapagliflozin/Metformin hydrochloride is not recommended in patients with an eGFR below 45 mL/min/1.73 m2.

Hepatic impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Dapagliflozin/Metformin hydrochloride is not recommended in patients with hepatic impairment (see section 4.4).

Elderly

No Dapagliflozin/Metformin hydrochloride dosage change is recommended based on age. More frequent assessment of renal function is recommended in elderly patients.

Paediatric population

The safety and efficacy of Dapagliflozin/Metformin hydrochloride in children and adolescents aged 0 to < 18 years have not yet been established. No data are available.

Discontinuation for iodinated contrast imaging procedures

Discontinue Dapagliflozin/Metformin hydrochloride at the time of, or prior to, an iodinated contrast imaging procedure in patients with a history of liver disease, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart Dapagliflozin/Metformin hydrochloride if renal function is stable (see section 4.4).

Method of administration

Dapagliflozin/Metformin hydrochloride tablet should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin.

4.3. Contraindications

Dapagliflozin/Metformin hydrochloride is contraindicated in patients with:

• hypersensitivity to the active substances or to any of the excipients listed in section 6.1

• severe renal impairment (eGFR below 30 mL/min/1.73 m2), end stage renal disease or patients on dialysis (see section 4.4)

• history of a serious hypersensitivity reaction to dapagliflozin, such as anaphylactic reactions or angioedema, or hypersensitivity to metformin HCl (see section 4.9).

• acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

4.4. Special warnings and precautions for use

Lactic acidosis

There have been post-marketing cases of metformin-associated lactic acidosis, including fatal cases. These cases had a subtle onset and were accompanied by nonspecific symptoms such as malaise, myalgias, abdominal pain, respiratory distress, or increased somnolence; however, hypothermia, hypotension and resistant bradyarrhythmias have occurred with severe acidosis.

Metformin-associated lactic acidosis was characterized by elevated blood lactate concentrations (>5 mmol/L), anion gap acidosis (without evidence of ketonuria or ketonemia), and an increased lactate: pyruvate ratio; metformin plasma levels

generally >5 mcg/mL. Metformin decreases liver uptake of lactate increasing lactate blood levels which may increase the risk of lactic acidosis, especially in patients at risk.

If metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immediate discontinuation of Dapagliflozin/Metformin hydrochloride.

In Dapagliflozin/Metformin hydrochloride-treated patients with a diagnosis or strong suspicion of lactic acidosis, prompt hemodialysis is recommended to correct the acidosis and remove accumulated metformin (metformin HCl is dialyzable, with a clearance of up to 170 mL/min under good hemodynamic conditions). Hemodialysis has often resulted in reversal of symptoms and recovery.

Educate patients and their families about the symptoms of lactic acidosis and if these symptoms occur instruct them to discontinue Dapagliflozin/Metformin hydrochloride and report these symptoms to their healthcare provider.

For each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metforminassociated lactic acidosis are provided below:

Renal Impairment

The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulation and metformin- (see sections 4.2, and 5.2).

• Before initiating Dapagliflozin/Metformin hydrochloride, obtain an estimated glomerular filtration rate (eGFR).

• Dapagliflozin/Metformin hydrochloride is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m2 (see section 4.3)

• Obtain an eGFR at least annually in all patients taking Dapagliflozin/Metformin hydrochloride. In patients at increased risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.

Drug Interactions

The concomitant use of Dapagliflozin/Metformin hydrochloride with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance or increase metformin accumulation (e.g., cationic drugs) (see section 4.5), Therefore, consider more frequent monitoring of patients.

Age 65 or Greater

The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients (see section 5.1).

Commented [MDR1]: Please complete this para Commented [MDR2]: in all places remove italic Radiological Studies with Contrast

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

Surgery and Other Procedures

Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment.

Dapagliflozin/Metformin hydrochloride should be temporarily discontinued while patients have restricted food and fluid intake.

Hypoxic States

Several of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue dapagliflozin and metformin HCl extended-release.

Excessive Alcohol Intake: Alcohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients against excessive alcohol intake while receiving Dapagliflozin/Metformin hydrochloride.

Hepatic Impairment

Patients with hepatic impairment have developed with cases of metforminassociated lactic acidosis. This may be due to impaired lactate clearance resulting in higher lactate blood levels. Therefore, avoid use of Dapagliflozin/Metformin hydrochloride in patients with clinical or laboratory evidence of hepatic disease.

Hypotension

Dapagliflozin causes intravascular volume contraction. Symptomatic hypotension can occur after initiating dapagliflozin (see section 4.9), particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m2), elderly patients, or patients on loop diuretics. Before initiating Dapagliflozin/Metformin hydrochloride in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms of hypotension after initiating therapy.

Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in patients with type 1 and type 2 diabetes mellitus taking sodium-glucose co transporter 2 (SGLT2) inhibitors, including dapagliflozin (see section 4.9). Fatal cases of ketoacidosis have been reported in patients taking dapagliflozin. Dapagliflozin/Metformin hydrochloride is not indicated for the treatment of patients with type 1 diabetes mellitus (see section 4.1).

Patients treated with Dapagliflozin/Metformin hydrochloride who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of blood glucose levels as ketoacidosis associated with Dapagliflozin/Metformin hydrochloride may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, Dapagliflozin/Metformin

hydrochloride should be discontinued, the patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid, and carbohydrate replacement.

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

Before initiating Dapagliflozin/Metformin hydrochloride, consider factors in the patient history that may predispose to ketoacidosis, including pancreatic insulin deficiency from any cause, caloric restriction and alcohol abuse.

For patients who undergo scheduled surgery, consider temporarily discontinuing Dapagliflozin/Metformin hydrochloride for at least 3 days prior to surgery (see sections 5.1 and 5.2).

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

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue Dapagliflozin/Metformin hydrochloride and seek medical attention immediately if signs and symptoms occur.

Acute kidney injury

Dapagliflozin causes intravascular volume contraction (see section 4.4), and can cause acute kidney injury. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving dapagliflozin.

Increases in serum creatinine and decreases in estimated GFR may also be observed with initiation of dapagliflozin. Elderly patients and patients with impaired renal function may be more susceptible to these changes. Before initiating dapagliflozin, consider

factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing dapagliflozin in the setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue dapagliflozin promptly and institute treatment.

Renal function should be evaluated prior to initiation of Dapagliflozin/Metformin hydrochloride and monitored periodically thereafter. Use of Dapagliflozin/Metformin hydrochloride is not recommended when the eGFR is less than 45 mL/min/1.73 m2.

Dapagliflozin/Metformin hydrochloride is contraindicated in patients with an eGFR

below 30 mL/min/1.73 m2 (see sections 4.2,4.3,4.4, and 5.1).

Urosepsis and pyelonephritis

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including dapagliflozin. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (see section 4.9)

Hypoglycemia with concomitant use with insulin and insulin secretagogues

Insulin and insulin secretagogues (e.g., sulfonylurea) are known to cause hypoglycemia. Dapagliflozin/Metformin hydrochloride may increase the risk of hypoglycemia when combined with insulin and/or an insulin secretagogue (see section 4.9). Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with Dapagliflozin/Metformin hydrochloride (see section 4.5)

Necrotizing fasciitis of the perineum (Fournier’s Gangrene)

Reports of necrotizing fasciitis of the perineum (Fournier’s Gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including dapagliflozin. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with Dapagliflozin/Metformin hydrochloride presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue Dapagliflozin/Metformin hydrochloride closely monitor blood glucose levels and provide appropriate alternative therapy for glycemic control.

Vitamin B12 concentrations

In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B12 absorption from the B12-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B12 supplementation. Certain individuals (those with inadequate vitamin B12 or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B12 levels. Measure hematologic parameters on an annual basis and vitamin B12 at 2-to 3-year intervals in patients on Dapagliflozin/Metformin hydrochloride and manage any abnormalities (see section 4.9)

Genital mycotic infections

Dapagliflozin increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections (see section 4.9). Monitor and treat appropriately.

4.5. Interaction with other medicinal products and other forms of interaction

Positive urine glucose test Dapagliflozin

Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) assay

Dapagliflozin

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

Carbonic anhydrase inhibitors

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

Drugs that reduce metformin clearance

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2]/multidrug and toxin extrusion [MATE] inhibitors, such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis (see section 5.2) Consider the benefits and risks of concomitant use.

Alcohol

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Warn patients against excessive alcohol intake while receiving Dapagliflozin/Metformin hydrochloride.

Drugs affecting glycemic control Metformin HCl

Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These medications include thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving Dapagliflozin/Metformin hydrochloride, observe the patient closely for loss of blood glucose control. When such drugs are withdrawn from a patient receiving Dapagliflozin/Metformin hydrochloride, observe the patient closely for hypoglycemia.

4.6. Fertility, pregnancy and lactation

Pregnancy

Based on animal data showing adverse renal effects, Dapagliflozin/Metformin hydrochloride is not recommended during the second and third trimesters of pregnancy.

Limited data with Dapagliflozin/Metformin hydrochloride or dapagliflozin in pregnant women are not sufficient to determine drug-associated risk for major birth defects or miscarriage.

Metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy.

Breastfeeding

There is no information regarding the presence of Dapagliflozin/Metformin hydrochloride or dapagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production.

Metformin is excreted in human milk in small amounts. A risk to the newborns/infants cannot be excluded.

This medicinal product should not be used while breast-feeding. Fertility

The effect of this medicinal product or dapagliflozin on fertility in humans has not been studied.

4.7. Effects on ability to drive and use machines

Dapagliflozin/Metformin hydrochloride has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when this medicinal product is used in combination with other glucose-lowering medicinal products known to cause hypoglycaemia.

4.8. Undesirable effects

Dapagliflozin plus Metformin Summary of the safety profile

Table 1 shows common adverse reactions associated with the use of dapagliflozin and metformin. These adverse reactions were not present at baseline, occurred more commonly on dapagliflozin and metformin than on placebo, and occurred in at least 2% of patients treated with either dapagliflozin 5 mg or dapagliflozin 10 mg.

Table 1: Adverse Reactions in Placebo-Controlled Studies Reported in ≥2% of Patients Treated with Dapagliflozin and Metformin

Adverse Reaction	% of Patients Pool of 8 Placebo-Controlled Studies Placebo and

Metformin N=1185 Dapagliflozin 5 mg and
Metformin N=410 Dapagliflozin 10 mg and Metformin N=983

Female genital mycotic infections* 1.5

Nasopharyngitis 5.9
Urinary tract infections†
Diarrhea 5.6 5.9 4.2 Headache 2.8 5.4 3.3 Male genital mycotic infections‡ 0

9.4 9.3

Influenza 2.4 Nausea 2.0 Back pain 3.2 Dizziness 2.2 Cough 1.9 Constipation

4.1 2.6
3.9 2.6
3.4 2.5
3.2 1.8
3.2 1.4
1.6 2.9 1.9

6.3 3.6

5.2
6.1 5.5

4.3 3.6

Dyslipidemia 1.4 2.7 1.5
Pharyngitis 1.1 2.7 1.5
Glucose < 54 mg/dL [n (%)] 43 (21.8) 55 (25.9) 45 (23.0)

* Severe episodes of hypoglycemia were defined as episodes of severe impairment in consciousness or behavior, requiring external (third party) assistance, and with prompt recovery after intervention regardless of glucose level.

† Episodes of hypoglycemia with glucose < 54 mg/dL (3 mmol/L) were defined as reported episodes of hypoglycemia meeting the glucose criteria that did not also qualify as a severe episode.

‡ OAD = oral antidiabetic therapy.

In the DECLARE study (see section 5.1), severe events of hypoglycemia were reported in 58 (0.7%) out of 8574 patients treated with dapagliflozin 10 mg and 83 (1.0%) out of 8569 patients treated with placebo.

Genital mycotic infections

Genital mycotic infections were more frequent with dapagliflozin treatment. Genital mycotic infections were reported in 0.9% of patients on placebo, 5.7% on dapagliflozin 5 mg, and 4.8% on dapagliflozin 10 mg, in the 12-study placebocontrolled pool. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with dapagliflozin 10 mg. Infections were more frequently reported in females than in males (see Table 2). The most frequently reported genital mycotic infections were vulvovaginal mycotic infections in females and balanitis in males. Patients with a history of genital mycotic infections were more likely to have a genital mycotic infection during the study than those with no prior history (10.0%, 23.1%, and 25.0% versus 0.8%, 5.9%, and 5.0% on placebo, dapagliflozin 5 mg, and dapagliflozin 10 mg, respectively). In the DECLARE study (see section 5.1), serious genital mycotic infections were reported in <0.1% of patients treated with dapagliflozin 10 mg and <0.1% of patients treated with placebo. Genital mycotic infections that caused study drug discontinuation were reported in 0.9% of patients treated with dapagliflozin 10 mg and <0.1% of patients treated with placebo.

Hypersensitivity reactions

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

Ketoacidosis

In the DECLARE study (see section 5.1), events of diabetic ketoacidosis (DKA) were reported in 27 out of 8574 patients in the dapagliflozin-treated group and in 12 out of 8569 patients in the placebo group. The events were evenly distributed over the study period.

Laboratory tests
Increases in Serum Creatinine and Decreases in eGFR

Dapagliflozin

Initiation of dapagliflozin causes an increase in serum creatinine and decrease in eGFR. In patients with normal or mildly impaired renal function at baseline, the serum

creatinine and and eGFR returned to baseline at Week 24. Sustained decreases in eGFR were seen in patients with moderate renal impairment (eGFR

30 to less than 60 mL/min/1.73 m2) (see sections 4.4 and 5.1) Increase in Hematocrit

Dapagliflozin

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

Increase in Low-Density Lipoprotein Cholesterol Dapagliflozin Dapagliflozin

In the pool of 13 placebo-controlled studies, changes from baseline in mean lipid values were reported in dapagliflozin-treated patients compared to placebo-treated patients. Mean percent changes from baseline at Week 24 were 0.0% versus 2.5% for total cholesterol, and -1.0% versus 2.9% for LDL cholesterol in the placebo and dapagliflozin 10 mg groups, respectively. In the DECLARE study (see section 5.1) mean changes from baseline after 4 years were

0.4 mg/dL versus -4.1 mg/dL for total cholesterol, and -2.5 mg/dL versus -4.4 mg/dL for LDL cholesterol, in dapagliflozin 10 mg-treated and the placebo groups, respectively.

Vitamin B12 Concentrations

Metformin HCl

In metformin clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B12 levels was observed in approximately 7% of patients.

Postmarketing experience Dapagliflozin

Additional adverse reactions have been identified during postapproval use of dapagliflozin. 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.

- Ketoacidosis

- Acute Kidney Injury
- Urosepsis and Pyelonephritis
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
- Rash

Metformin HCl
• Cholestatic, hepatocellular, and mixed hepatocellular liver injury Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the local reporting system.

4.9. Overdose

Dapagliflozin

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

Metformin

Overdose of metformin HCl has occurred, including ingestion of amounts >50 grams. Lactic acidosis has been reported in approximately 32% of metformin overdose cases (see section 4.4). Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of

accumulated drug from patients in whom metformin overdosage is suspected.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties Mechanism of action

Dapagliflozin and metformin HCl extended-release combines two antihyperglycemic agents with complementary mechanisms of action to improve glycemic control in

patients with type 2 diabetes: dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and metformin HCl, a biguanide.

Dapagliflozin

Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion. Dapagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to, lowering both pre-and afterload of the heart and downregulation of sympathetic activity.

Metformin

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.

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 (see Figure 1). Dapagliflozin doses of 5 or 10 mg per day in patients with type 2 diabetes mellitus for 12 weeks resulted in excretion of approximately 70 grams of glucose in the urine per day. A near maximum glucose excretion was observed at the dapagliflozin daily dose of 20 mg. This urinary glucose excretion with dapagliflozin also results in increases in urinary volume (see section 4.9). After discontinuation of dapagliflozin, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg dose.

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

The coadministration of dapagliflozin and metformin XR tablets has been studied in treatment-naive patients inadequately controlled on diet and exercise alone. The coadministration of dapagliflozin and metformin IR or XR tablets has been studied in patients with type 2 diabetes inadequately controlled on metformin and compared with a sulfonylurea (glipizide) in combination with metformin. Treatment with dapagliflozin plus metformin at all doses produced clinically relevant and statistically significant

improvements in HbA1c and fasting plasma glucose (FPG) compared to placebo in combination with metformin (initial or add-on therapy). HbA1c reductions were seen across subgroups including gender, age, race, duration of disease, and baseline body mass index (BMI).

Initial combination therapy with metformin extended-release

A total of 1236 treatment-naive patients with inadequately controlled type 2 diabetes (HbA1c ≥7.5% and ≤12%) participated in 2 active-controlled studies of

24-week duration to evaluate initial therapy with dapagliflozin 5 mg (NCT00643851) or 10 mg (NCT00859898) in combination with metformin extended-release (XR) formulation.

In one study, 638 patients randomized to 1 of 3 treatment arms following a 1-week lead-in period received: dapagliflozin 10 mg plus metformin XR (up to 2000 mg/day), dapagliflozin 10 mg plus placebo, or metformin XR (up to 2000 mg/day) plus placebo. Metformin XR dose was up-titrated weekly in 500 mg increments, as tolerated, with a median dose achieved of 2000 mg.

The combination treatment of dapagliflozin 10 mg plus metformin XR provided statistically significant improvements in HbA1c and FPG compared with either of the monotherapy treatments and statistically significant reduction in body weight compared with metformin XR alone (see Table 5 and Figure 2). Dapagliflozin 10 mg as monotherapy also provided statistically significant improvements in FPG and statistically significant reduction in body weight compared with metformin alone and was noninferior to metformin XR monotherapy in lowering HbA1c.

Table 5: Results at Week 24 (LOCF) in an Active-Controlled Study of Dapagliflozin Initial Combination Therapy with Metformin XR

Efficacy Parameter Dapagliflozin
10 mg +
Metformin XR
N=211† Dapaglifloz in 10 mg N=219† HbA1c (%)

Metformi n XR N=208†

Baseline (mean) 9.1 9.0 9.0
Change from baseline (adjusted mean‡)
Difference from dapagliflozin (adjusted mean‡) (95% CI) −0.5§ (−0.7, −0.3)
Difference from metformin XR (adjusted mean‡) (95% CI) −0.5§ (−0.8, −0.3) 0.0¶ (−0.2, 0.2)

Percent of patients achieving
HbA1c <7%
adjusted for baseline 46.6%
FPG (mg/dL)
Baseline (mean) 189.6
Change from baseline (adjusted mean‡)
Difference from dapagliflozin (adjusted mean‡) (95% CI) −13.9§ (−20.9, −7.0)
Difference from metformin XR (adjusted mean‡) (95% CI) −25.5§

(−32.6, −18.5)
Body Weight (kg)
Baseline (mean) 88.6 88.5 87.2
Change from baseline (adjusted mean‡) −3.3 −2.7 −1.4 Difference from metformin XR

31.7% 197.5

35.2%

−2.0 −1.5 −1.4

189.9
−60.4 −46.4

−34.8

(adjusted mean‡) (95% CI) −2.0§

(−2.6, −1.3) −1.4§

(−2.0, −0.7)

* 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. Noninferior versus metformin XR. # p-value <0.05.

Figure 2: Adjusted Mean Change from Baseline Over Time in HbA1c (%) in a 24-Week Active-Controlled Study of Dapagliflozin Initial Combination Therapy with Metformin XR

In the second study, 603 patients were randomized to 1 of 3 treatment arms following a 1-week lead-in period: dapagliflozin 5 mg plus metformin XR (up to 2000 mg/day),

dapagliflozin 5 mg plus placebo, or metformin XR (up to 2000 mg/day) plus placebo. Metformin XR dose was up-titrated weekly in 500 mg increments, as tolerated, with a median dose achieved of 2000 mg.

The combination treatment of dapagliflozin 5 mg plus metformin XR provided statistically significant improvements in HbA1c and FPG compared with either of the monotherapy treatments and statistically significant reduction in body weight compared with metformin XR alone (see Table 6).

Table 6: Results at Week 24 (LOCF) in an Active-Controlled Study of Dapagliflozin Initial Combination Therapy with Metformin XR

Efficacy Parameter Dapagliflozi n 5 mg + Metformin

XR N=194† Dapaglifloz in 5 mg N=203† HbA1c (%)
Baseline (mean) 9.2 9.1 9.1 Change from baseline (adjusted mean‡) Difference from dapagliflozin

(adjusted mean‡) (95% CI) −0.9§ (−1.1, −0.6)

Metformin XR N=201†

−2.1 −1.2 −1.4

Difference from metformin XR
(adjusted mean‡) (95% CI) −0.7§
(−0.9, −0.5)
Percent of patients achieving
HbA1c <7% adjusted for baseline 52.4%¶
FPG (mg/dL)
Baseline (mean) 193.4 190.8 196.7 Change from baseline (adjusted mean‡) −61.0
Difference from dapagliflozin (adjusted mean‡) (95% CI) (−26.7, −11.4)
Difference from metformin XR (adjusted mean‡) (95% CI) (−35.1, −19.8)
Body Weight (kg)
Baseline (mean) 84.2 86.2 85.8
Change from baseline (adjusted mean‡) −2.7 −2.6 Difference from metformin XR (adjusted mean‡) (95% CI)

* 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. p-value <0.05.

Add-On to Metformin Immediate-Release

A total of 546 patients with type 2 diabetes with inadequate glycemic control

(HbA1c ≥7% and ≤10%) participated in a 24-week, placebo-controlled study to evaluate dapagliflozin in combination with metformin (NCT00528879). Patients on metformin at a dose of at least 1500 mg/day were randomized after completing a

22.5%

34.6%

−42.0 −33.6 −19.1§

−27.5§

−1.3
−1.4§ (−2.0, −0.7)

2-week, single-blind, placebo lead-in period. Following the lead-in period, eligible patients were randomized to dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo in addition to their current dose of metformin.

As add-on treatment to metformin, dapagliflozin 10 mg provided statistically significant improvements in HbA1c and FPG, and statistically significant reduction in body weight compared with placebo at Week 24 (see Table 7 and Figure 3). Statistically significant ($p<0.05$ for both doses) mean changes from baseline in systolic blood pressure relative to placebo plus metformin were −4.5 mmHg and −5.3 mmHg with dapagliflozin 5 mg and 10 mg plus metformin, respectively.

Table 7: Results of a 24-Week (LOCF*) Placebo-Controlled Study of Dapagliflozin in Add-On Combination with Metformin

Efficacy Parameter Dapagliflozin 10 mg +
Metformin
N=135†

5 mg +
Metformin
N=137†
Metformin
N=137†

HbA1c (%)
Baseline (mean) 7.9 8.2 8.1 Change from baseline (adjusted mean‡) Difference from placebo

(adjusted mean‡) (95% CI) −0.5§ (−0.7,

−0.3)

Dapagliflozin

Placebo +

Percent of patients achieving HbA1c <7% adjusted for baseline 37.5%¶ 25.9%

FPG (mg/dL)
Baseline (mean) 156.0 169.2 165.6

40.6%¶

−0.8 −0.7 −0.3

Change from baseline at Week
24 (adjusted mean‡) −23.5 −21.5 −6.0 Difference from placebo
(adjusted mean‡) (95% CI) −17.5§ (−25.0,
−10.0)
Change from baseline at Week
1 (adjusted mean‡) −16.5§
(N=115) −12.0§
(N=121) 1.2
(N=126)
Body Weight (kg)
Baseline (mean) 86.3 84.7
Change from baseline
(adjusted mean‡) −2.9 −3.0
Difference from placebo
(adjusted mean‡) (95% CI)
−1.3) −2.2§(−2.8,
−1.5)

* 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 versus placebo + metformin. p-value <0.05 versus placebo + metformin.

from baseline in systolic blood pressure relative to glipizide plus metformin was −5.0 mmHg with dapagliflozin plus metformin.

Table 8: Results at Week 52 (LOCF*) in an Active-Controlled Study Comparing Dapagliflozin to Glipizide as Add-On to Metformin

87.7
−0.9
−2.0§ (−2.6,

Efficacy Parameter Dapagliflozin +

Metformin N=400† Glipizide + Metformin N=401†

HbA1c (%)
Baseline (mean) 7.7 7.7
Change from baseline adjusted mean‡) −0.5

−0.5

Difference from glipizide + metformin (adjusted mean‡)
(95% CI) 0.0§
(−0.1, 0.1)

Body Weight (kg)
Baseline (mean) 88.4 87.6
Change from baseline
(adjusted mean‡) −3.2 1.4
Difference from glipizide + metformin (adjusted mean‡) (95% CI) −4.7¶ (−5.1, −4.2)

* LOCF: last observation carried forward.

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

‡ Least squares mean adjusted for baseline value. § Noninferior to glipizide + metformin. p-value <0.0001.

Use in patients with type 2 diabetes and moderate renal impairment

Dapagliflozin was assessed in two placebo-controlled studies of patients with type 2 diabetes and moderate renal impairment.

Patients with type 2 diabetes and an eGFR between 45 to less than 60 mL/min/1.73 m2 inadequately controlled on current diabetes therapy participated in a 24-week, double-blind, placebo-controlled clinical study (NCT02413398). Patients were randomized to either dapagliflozin 10 mg or placebo, administered orally once daily. At Week 24, dapagliflozin provided statistically significant reductions in HbA1c compared with placebo (Table 9).

Table 9: Results at Week 24 of Placebo-Controlled Study for Dapagliflozin in Patients with Type 2 Diabetes and Renal Impairment (eGFR 45 to less than 60 mL/min/1.73 m2)

Dapagliflozin 10 mg Number of patients:

Placebo N=160 N=161

HbA1c (%)
Baseline (mean) 8.3
Change from baseline (adjusted mean*) -0.4 -0.1 Difference from placebo
(adjusted mean*) (95% CI) -0.3†
(-0.5, -0.1)

*Least squares mean adjusted for baseline value; at Week 24, HbA1c was missing for 5.6% and 6.8% of individuals treated with dapagliflozin and placebo, respectively. Retrieved dropouts, i.e. observed HbA1c at Week 24 from subjects who discontinued treatment, were used to impute missing values in HbA1c.

† p-value =0.008 versus placebo.

8.0

Cardiovascular outcomes in patients with type 2 diabetes mellitus

Dapagliflozin Effect on Cardiovascular Events (DECLARE, NCT01730534) was an international, multicenter, randomized, double-blind, placebo-controlled, clinical study conducted to determine the effect of dapagliflozin 10 mg relative to placebo on CV outcomes when added to current background therapy. All patients had type 2 diabetes mellitus and either established CVD or two or more additional CV risk factors (age ≥55 years in men or ≥60 years in women and one or more of dyslipidemia, hypertension, or current tobacco use).Concomitant antidiabetic and atherosclerotic therapies could be adjusted, at the discretion of investigators, to ensure participants were treated according to the standard care for these diseases.

Of 17160 randomized patients, 6974 (40.6%) had established CVD and 10186 (59.4%) did not have established CVD. A total of 8582 patients were randomized to dapagliflozin 10 mg, 8578 to placebo, and patients were followed for a median of 4.2 years.

Approximately 80% of the trial population was White, 4% Black or African-American, and 13% Asian. The mean age was 64 years, and approximately 63% were male.

Mean duration of diabetes was 11.9 years and 22.4% of patients had diabetes for less than

5 years. Mean eGFR was 85.2 mL/min/1.73 m2. At baseline, 23.5% of patients had microalbuminuria (UACR ≥30 to ≤300 mg/g) and 6.8% had macroalbuminuria

(UACR
>300 mg/g). Mean HbA1c was 8.3% and mean BMI was 32.1 kg/ m2. At baseline, 10% of patients had a history of heart failure.

Most patients (98.1%) used one or more diabetic medications at baseline. 82.0% of the patients were being treated with metformin, 40.9% with insulin, 42.7% with a sulfonylurea, 16.8% with a DPP4 inhibitor, and 4.4% with a GLP-1 receptor agonist.

Approximately 81.3% of patients were treated with angiotensin converting enzyme inhibitors or angiotensin receptor blockers, 75.0% with statins, 61.1% with antiplatelet therapy, 55.5% with acetylsalicylic acid, 52.6% with beta-blockers, 34.9% with calcium channel blockers, 22.0% with thiazide diuretics, and 10.5% with loop diuretics.

A Cox proportional hazards model was used to test for non-inferiority against the pre-specified risk margin of 1.3 for the hazard ratio (HR) of the composite of CV death, myocardial infarction (MI), or ischemic stroke and to test for superiority on the dual primary endpoints: the composite of hospitalization for heart failure or CV death, and MACE, if non-inferiority was demonstrated.

The incidence rate of MACE was similar in both treatment arms: 2.3 MACE events per 100 patient-years on dapagliflozin vs. 2.46 MACE events per 100 patient-years on placebo. The estimated hazard ratio of MACE associated with dapagliflozin relative to placebo was 0.93 with a 95.38% confidence interval of (0.84,1.03). The upper bound of this confidence interval, 1.03, excluded a risk margin larger than 1.3.

Dapagliflozin 10 mg was superior to placebo in reducing the incidence of the primary composite endpoint of hospitalization for heart failure or CV death (HR 0.83 [95% CI 0.73, 0.95]).

The treatment effect was due to a significant reduction in the risk of hospitalization for heart failure in subjects randomized to dapagliflozin 10 mg (HR 0.73 [95% CI 0.61, 0.88]), with no change in the risk of CV death (Table 10 and Figures 4 and 5).

Table 10: Treatment Effects for the Primary Endpoints* and Their Components* in the DECLARE Study

Patients with events n(%)

Efficacy Variable (time to first occurrence 10 mg N=8582

Placebo N=8578

Hazard Ratio (95% CI)

Primary Endpoints

Dapagliflozin

Composite of Hospitalization for Heart Failure, CV Death† 0.83 (0.73,

417 (4.9)

496 (5.8)

0.95)

Composite Endpoint of CV Death, MI, Ischemic Stroke 0.93 (0.84,

1.03)
Components of the composite endpoints‡ Hospitalization for Heart Failure 212 (2.5) 286 (3.3) 0.88)
CV Death 245 (2.9)
1.17)
Myocardial Infarction
1.01)
Ischemic Stroke

235 (2.7) 231 (2.7) 1.01 (0.84, 1.21)

756 (8.8)

0.73 (0.61,

803 (9.4)

249 (2.9) 393 (4.6)

0.98 (0.82, 441 (5.1)

0.89 (0.77,

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

* Full analysis set.
† p-value =0.005 versus placebo
‡ total number of events presented for each component of the composite endpoints

Figure 4: Time to First Occurrence of Hospitalization for Heart Failure or CV Death in the DECLARE Study

Figure 5: Time to First Occurrence of Hospitalization for Heart Failure in the DECLARE Study

5.2. Pharmacokinetic properties

Dapagliflozin/Metformin hydrochloride

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

Absorption Dapagliflozin

Following oral administration of dapagliflozin, the maximum plasma concentration

(Cmax) is usually attained within 2 hours under fasting state. The Cmax and AUC values increase dose proportionally with increase in dapagliflozin dose in the therapeutic dose range. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Administration of dapagliflozin with a high-fat meal decreases its Cmax by up to 50% and prolongs Tmax by approximately 1 hour, but does not alter AUC as compared with the fasted state. These changes are not

considered to be clinically meaningful and dapagliflozin can be administered with or without food.

Metformin HCl
Following a single oral dose of metformin extended-release, Cmax is achieved with a

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

Distribution Dapagliflozin

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

Metformin HCl

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

Biotransformation Dapagliflozin

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

Metformin HCl

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

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

Dapagliflozin

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [14C]-dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively. In urine, less than 2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life (t1⁄2) for dapagliflozin is approximately 12.9 hours following a single oral dose of dapagliflozin 10 mg.

Metformin HCl

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

Specific Populations

Renal Impairment Dapagliflozin

At steady-state (20 mg once daily dapagliflozin for 7 days), patients with type 2 diabetes with mild, moderate, or severe renal impairment (as determined by eGFR) had geometric mean systemic exposures of dapagliflozin that were 45%, 2.04-fold, and 3.03-fold higher, respectively, as compared to patients with type 2 diabetes with normal renal function. Higher systemic exposure of dapagliflozin in patients with type

2 diabetes mellitus with renal impairment did not result in a correspondingly higher 24-hour urinary glucose excretion. The steady-state 24-hour urinary glucose excretion in patients with type 2 diabetes and mild, moderate, and severe renal impairment was 42%, 80%, and 90% lower, respectively, than patients with type 2 diabetes with normal renal function. The impact of hemodialysis on dapagliflozin exposure is not known (see sections 4.2,4,4 and 5.1).

Metformin HCl

In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased. (see sections 4.3 and 4.4).

Hepatic Impairment

Dapagliflozin

In patients with mild and moderate hepatic impairment (Child-Pugh classes A and B), mean Cmax and AUC of dapagliflozin were up to 12% and 36% higher, respectively, as compared to healthy matched control subjects following single-dose

administration of 10 mg dapagliflozin. These differences were not considered to be clinically meaningful. In patients with severe hepatic impairment (Child-Pugh class C),

mean Cmax and AUC of dapagliflozin were up to 40% and 67% higher, respectively, as compared to healthy matched controls.

Metformin HCl

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

Elderly Dapagliflozin

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

Metformin HCl

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

Pediatric population

Pharmacokinetics of dapagliflozin/metformin hydrochloride in the pediatric population has not been studied.

Gender Dapagliflozin

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

Metformin HCl

Metformin pharmacokinetic parameters did not differ significantly between healthy subjects and patients with type 2 diabetes when analyzed according to gender

(males=19, females=16). Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of metformin was comparable in males and females.

Race

Dapagliflozin

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

Metformin HCl

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

Body Weight Dapagliflozin

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

Drug Interactions

Specific pharmacokinetic drug interaction studies with dapagliflozin/metformin hydrocloride have not been performed, although such studies have been conducted with the individual dapagliflozin and metformin components.

In vitro assessment of drug interactions Dapagliflozin

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

Effects of other drugs on metformin

Table 11 shows the effect of other coadministered drugs on metformin.
Table 11: Effect of Coadministered Drug on Plasma Metformin Systemic Exposure

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

Metformin

Cmax
No dosing adjustments required for the following: Glyburide (5 mg) 850 mg ↓9%§ ↓7%§ Furosemide (40 mg) 850 mg ↑15%§ Nifedipine (10 mg) 850 mg ↑9% ↑20%

↑22%§

Simvastatin (40 mg)

Simvastatin (40 mg) Simvastatin (40 mg)

Simvastatin (40 mg)

Digoxin (0.25 mg) Digoxin (0.25 mg) Digoxin (0.25 mg) Digoxin (0.25 m g)

Warfarin (25 mg) Swarfarin R-warfarin Warfarin (25 mg) Swarfarin R-warfarin Warfarin (25 mg) Swarfarin R-warfarin Warfarin (25 mg) S-warfarin Rwarfarin

* Single dose unless otherwise noted.

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

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

Preclinical safety data

Carcinogenesis, mutagenesis, impairment of fertility Dapagliflozin/Metformin hydrochloride

No animal studies have been conducted with dapagliflozin and metformin HCl extended-release to evaluate carcinogenesis, mutagenesis, or impairment of fertility. The following data are based on the findings in the studies with dapagliflozin and metformin individually.

Dapagliflozin

Dapagliflozin did not induce tumors in either mice or rats at any of the doses evaluated in 2-year carcinogenicity studies. Oral doses in mice consisted of 5, 15, and 40 mg/kg/day in males and 2, 10 and 20 mg/kg/day in females, and oral doses in rats were 0.5, 2, and 10 mg/kg/day for both males and females. The highest doses evaluated in mice were approximately 72-times (males) and 105-times (females) the clinical dose of 10 mg per day, based on AUC exposure. In rats, the highest dose was approximately 131-times (males) and 186-times (females) the clinical dose of 10 mg per day, based on AUC exposure.

Dapagliflozin was negative in the Ames mutagenicity assay and was positive in a series of in vitro clastogenicity assays in the presence of S9 activation and at concentrations greater than or equal to 100 µg/mL. Dapagliflozin was negative for clastogenicity in a series of in vivo studies evaluating micronuclei or DNA repair in rats at exposure multiples greater than 2100-times the clinical dose. There was no carcinogenicity or mutagenicity signal in animal studies, suggesting that dapagliflozin does not represent a genotoxic risk to humans.

Dapagliflozin had no effects on mating, fertility, or early embryonic development in treated male or female rats at exposure multiples less than or equal to 1708-times and 998-times the maximum recommended human dose in males and females, respectively.

Metformin HCl

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

5.3.

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

There was no evidence of a mutagenic potential of metformin in the following in vitro tests: Ames test (S. typhimurium), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the in vivo mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately 3 times the maximum recommended human dose based on body surface area comparisons

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose, Mannitol,
Copovidone,
Isopropyl alcohol,
Crospovidone,
Silicon dioxide,
Magnesium stearate,
Carboxy methylcellulose sodium, Hypromellose.

The 5 mg/500 mg and 5/1000 mg of XIGDUO also contain ferric oxide red.

The 5 mg/500 mg and 10 mg/500 mg of XIGDUO also contain hypromellose. The 10 mg/500 mg and 10 mg/1000 of XIGDUO also contain ferric oxide yellow.

Film-coating Polyvinyl alcohol,

Titanium dioxide,

Macrogol/PEG, Talc.

Additionally, the film coating for XIGDUO 5 mg/500 mg contain ferrosoferric oxide/black iron oxide.

XIGDUO 10 mg/500 mg contains FD&C blue/indigo carmine AL 3%-5%. XIGDUO 5 mg/500 mg, and 10 mg/1000 mg contains iron oxide red. XIGDUO 5 mg/500 mg and 10 mg/500 mg contain iron oxide yellow. XIGDUO 5 mg/1000 mg contains iron oxide yellow and iron oxide red. 6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

30's Count: 100cc white HDPE container with 38 mm white child resistant cap.

6.6 Special precautions for disposal

No special requirements for disposal.

6.7 Prescription and dispensing conditions: List I: Strictly under prescription Prescription only Medicine

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

AstraZeneca UK Limited -

Silk Road Business Park

Charter Way Macclesfield Cheshire SK 10 2NA

United Kingdom

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10. DATE OF REVISION OF THE TEXT

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