

## PRODUCT MONOGRAPH

 **FORXIGA<sup>®</sup>**

dapagliflozin tablets

(as dapagliflozin propanediol monohydrate)

5 mg and 10 mg

ATC Code: A10BK01

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

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**Pr**FORXIGA®

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(as dapagliflozin propanediol monohydrate)

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet / 5 mg, 10 mg	Lactose <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i>

### INDICATIONS AND CLINICAL USE

#### Type 2 Diabetes Mellitus (T2DM)

**Monotherapy:** FORXIGA (dapagliflozin) is indicated for use as an adjunct to diet and exercise to improve glycemic control in adult patients with T2DM for whom metformin is inappropriate due to contraindications or intolerance.

**Add-on combination:** FORXIGA is indicated in adult patients with T2DM to improve glycemic control in combination with

- metformin
- a sulfonylurea
- metformin and a sulfonylurea
- sitagliptin (alone or with metformin)
- insulin (alone or with metformin)

when metformin alone or the existing therapy listed above, along with diet and exercise, do not provide adequate glycemic control (see CLINICAL TRIALS).

**Add-On Combination in Patients with Cardiovascular Risk Factors or Established Cardiovascular Disease:** FORXIGA is indicated as an adjunct to diet, exercise, and standard of care therapy to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and CV risk factors or established CV disease (see CLINICAL TRIALS).

**Geriatrics (≥65 years of age):** No dosage adjustment is required in patients ≥65 years of age. FORXIGA should be used with caution in this population as a higher proportion of patients ≥65 years of age treated with FORXIGA 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).

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

### **Heart Failure (DAPA-HF)**

FORXIGA is indicated in adults, as an adjunct to standard of care therapy, for the treatment of heart failure with reduced ejection fraction (HFrEF) to reduce the risk of cardiovascular (CV) death, hospitalization for heart failure and urgent heart failure visit (see CLINICAL TRIALS).

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

## **CONTRAINDICATIONS**

FORXIGA (dapagliflozin) is contraindicated in:

- Patients with a history of hypersensitivity reaction to the active substance or to any of the excipients. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.
- Patients with an eGFR less than 30 mL/min/1.73m<sup>2</sup>, end-stage renal disease (ESRD) or patients on dialysis (see WARNINGS AND PRECAUTIONS, Renal).

## **WARNINGS AND PRECAUTIONS**

### **Serious Warnings and Precautions**

#### **Diabetic Ketoacidosis in Patients with Diabetes**

- Clinical trial and post-market cases of diabetic ketoacidosis (DKA), a serious life-

threatening condition requiring urgent hospitalization, have been reported in patients with T2DM treated with FORXIGA (dapagliflozin) and other sodium-glucose co-transporter 2 (SGLT2) inhibitors. A number of these cases have been atypical with blood glucose values below 13.9 mmol/L (250 mg/dL) (see ADVERSE REACTIONS). Some cases of DKA have been fatal.

- Patients should be assessed for DKA 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, FORXIGA should be **discontinued immediately**.
- FORXIGA should not be used for the treatment of DKA or in patients with a history of DKA.
- FORXIGA is not indicated, and should not be used, in patients with type 1 diabetes.

### **Cardiovascular**

#### **Use in patients at risk for volume depletion, hypotension and/or electrolyte imbalances:**

Due to its mechanism of action, dapagliflozin causes osmotic diuresis that may be associated with decreases in blood pressure, which may be more pronounced in patients with high blood glucose concentrations.

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

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

Careful monitoring of volume status is recommended. Temporary interruption of FORXIGA may be considered for patients who develop volume depletion until the depletion is corrected (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, and ADVERSE REACTIONS).

### **Endocrine and Metabolism**

**Diabetic ketoacidosis in patients with diabetes:** Clinical trial and post-market cases of DKA, a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with T2DM treated with FORXIGA 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.

FORXIGA is not indicated, and should not be used, in patients with type 1 diabetes. The diagnosis of T2DM should therefore be confirmed before initiating FORXIGA as a treatment to improve glycemic control.

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 FORXIGA treatment and be assessed for DKA immediately.**

Interruption of treatment with FORXIGA 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 FORXIGA 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).

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

**Increases in Low-Density Lipoprotein (LDL-C):** Dose-related increases in LDL-C are seen with FORXIGA treatment (see ADVERSE REACTIONS). LDL-C levels should be monitored.

### **Genitourinary**

**Genital mycotic infections:** Patients, particularly those with a history of genital mycotic infections, should be advised that FORXIGA increases the risk of genital mycotic infections (see ADVERSE REACTIONS).

**Urinary tract infections (including urosepsis and pyelonephritis):** Treatment with FORXIGA 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 FORXIGA. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated.

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

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

## **Hematologic**

**Elevated hemoglobin and hematocrit:** Mean hemoglobin and hematocrit increased in patients administered FORXIGA, as did the number of patients with abnormally elevated values for hemoglobin/hematocrit (see ADVERSE REACTIONS). FORXIGA should be used with caution in patients with an elevated hematocrit.

## **Hepatic/Biliary/Pancreatic**

Elevations in hepatic transaminases have been reported in dapagliflozin treated patients in clinical trials; however, a causal relationship with dapagliflozin has not been established. FORXIGA exposure is increased in patients with severe hepatic impairment (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY). Use of FORXIGA is not recommended in patients with severe hepatic impairment.

## **Renal**

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

### **Type 2 Diabetes Mellitus**

Post-marketing cases of acute kidney injury, including acute renal failure, shortly after the initiation of FORXIGA treatment have been reported in T2DM patients (see ADVERSE REACTIONS). Patients with hypovolemia may be more susceptible to these changes (see ADVERSE REACTIONS).

Renal function should be assessed prior to initiation of FORXIGA and regularly thereafter, with more frequent monitoring in patients whose eGFR decreases to  $<60 \text{ mL/min/1.73m}^2$ .

FORXIGA is not recommended for use in patients with T2DM, being treated for glycemic control, with an eGFR persistently  $<45 \text{ mL/min/1.73m}^2$ , severe renal impairment, ESRD, or patients on dialysis as the glycemic efficacy of dapagliflozin is dependent on renal function (see ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, and CLINICAL TRIALS). In such patients, FORXIGA did not improve glycemic control and adverse reactions were more frequent (see ADVERSE REACTIONS). FORXIGA is contraindicated in patients with an eGFR less than  $30 \text{ mL/min/1.73m}^2$ , ESRD or patients on dialysis (see CONTRAINDICATIONS).

Before initiating FORXIGA, 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 FORXIGA in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue FORXIGA promptly and institute treatment.

## Heart Failure (DAPA-HF)

There is limited experience with FORXIGA in patients with severe renal impairment (eGFR <30 mL/min/1.73m<sup>2</sup>) or ESRD. FORXIGA is contraindicated in patients with an eGFR less than 30 mL/min/1.73m<sup>2</sup>, ESRD or patients on dialysis (see CONTRAINDICATIONS).

### Special Populations

**Pregnant Women:** FORXIGA must not be used in pregnancy. 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).

There are no adequate and well-controlled studies of FORXIGA in pregnant women. When pregnancy is detected, FORXIGA should be discontinued.

**Nursing Women:** FORXIGA must not be used by a nursing woman. Studies in rats have shown excretion of FORXIGA in milk. Direct and indirect exposure of FORXIGA 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, FORXIGA-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 FORXIGA must be avoided during the first 2 years of life (see TOXICOLOGY).

It is not known whether FORXIGA and/or its metabolite are excreted in human milk.

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

**Geriatrics (≥65 years of age):** 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 FORXIGA in improving glycemic control. After controlling for renal function (eGFR), there was no conclusive evidence suggesting that age is an independent factor affecting efficacy. No dosage adjustment is required in patients ≥65 years of age. In patients ≥65 years of age, a higher proportion of patients treated with FORXIGA had adverse events related to volume depletion and renal impairment or failure compared with placebo. The most commonly reported adverse events related to renal impairment or failure in patients ≥65 years of age in any treatment group were creatinine renal clearance decreased, renal impairment, and increased blood creatinine.



Older patients are more likely to have impaired renal function (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, Renal Function, and ADVERSE REACTIONS).

### **Monitoring and Laboratory Tests**

**Blood glucose and HbA1c:** Response to FORXIGA treatment in T2DM patients should be monitored by periodic measurements of blood glucose and HbA1c levels.

Due to its mechanism of action, patients taking FORXIGA will test positive for glucose in their urine (see DRUG INTERACTIONS, Drug-Laboratory Interactions).

**Renal function:** Renal function should be assessed prior to initiation of FORXIGA and regularly thereafter. FORXIGA is not recommended for use in patients with T2DM, being treated for glycemic control, with an eGFR persistently  $<45$  mL/min/1.73m<sup>2</sup>, severe renal impairment, ESRD, or patients on dialysis as the glycemic efficacy of dapagliflozin is dependent on renal function (see ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, and CLINICAL TRIALS). FORXIGA is contraindicated in patients with an eGFR less than 30 mL/min/1.73m<sup>2</sup>, ESRD or patients on dialysis (see CONTRAINDICATIONS).

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:** FORXIGA is not recommended for use in patients who are volume depleted (see DOSAGE AND ADMINISTRATION). Before initiating FORXIGA, 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 FORXIGA. In these patients, careful monitoring of volume status (e.g., physical examination, blood pressure measurements, laboratory tests, including hematocrit, serum electrolytes and renal function tests) is recommended. If volume depletion develops, temporary interruption of treatment with FORXIGA may be considered until fluid loss is corrected.

**LDL-cholesterol:** LDL-C levels should be measured at baseline and at regular intervals during treatment with FORXIGA due to dose-dependent increases in LDL-C seen with therapy.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

*Clinical trials of FORXIGA to improve glycemic control*

The overall incidence of adverse events in a 12-study, short-term, placebo-controlled pool (short-term treatment) in T2DM patients treated with FORXIGA 5 mg and 10 mg for glycemic control was 61.9% and 61.5%, respectively compared to 56.9% for the placebo group.

The most commonly reported adverse events during treatment with FORXIGA 5 mg or 10 mg ( $\geq 5\%$ ) were female genital mycotic infections, nasopharyngitis and urinary tract infections. Discontinuation of therapy due to adverse events in patients who received FORXIGA 5 mg and 10 mg was 2.8% and 3.2%, respectively, compared to 2.5% for the placebo group. The most commonly reported events leading to discontinuation and reported in at least three (3) FORXIGA 10 mg-treated patients were renal impairment (0.8%), decrease in creatinine clearance (0.6%), increased blood creatinine (0.3%), urinary tract infections (0.2%), and vulvovaginal mycotic infection (0.1%).

A total of 10 serious adverse drug events, assessed as related by the investigator, were reported in 9 patients in the short-term, placebo-controlled pool: 2 reports from patients taking FORXIGA 5 mg daily (change of bowel habit, hypoglycemia), 2 reports from patients taking FORXIGA 10 mg daily (constipation, rotator cuff syndrome) and 6 reports from patients in the placebo group (thrombocytopenia, acute myocardial infarction, cystitis, pyelonephritis, overdose and loss of consciousness).

#### *Cardiovascular outcomes trial (DECLARE-TIMI 58)*

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

#### **Heart Failure (DAPA-HF)**

In the dapagliflozin CV outcome study in patients with HFrEF (DAPA-HF), 2368 patients were treated with dapagliflozin 10 mg and 2368 patients with placebo for a median exposure time of 18 months.

The numbers of patients with serious adverse events were fewer in the dapagliflozin treatment group compared with the placebo group: 35.7% vs 40.2%, respectively. The three most commonly reported serious adverse events in both treatment groups were cardiac failure, pneumonia and cardiac failure congestive. Discontinuations due to adverse events were low and balanced between patients on dapagliflozin treatment versus placebo (4.7% vs. 4.9%, respectively). The most common adverse events leading to permanent discontinuation of FORXIGA 10 mg were cardiac failure, dizziness and hypotension for the dapagliflozin treatment group and cardiac failure, cardiac failure congestive and renal impairment for the placebo group.

## **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.*

FORXIGA has been evaluated in clinical trials in patients with T2DM and in patients with HFrEF. The overall safety profile of FORXIGA was consistent across the studied dapagliflozin indications. DKA was observed only in patients with T2DM.

### **Clinical Trials in Patients with T2DM Treated for Glycemic Control**

Three major pools of patients with T2DM, who were being treated for glycemic control, were used to evaluate adverse reactions with FORXIGA 5 mg and 10 mg versus control, including two placebo-controlled study pools and a larger pool of active- and placebo-controlled studies. In addition, adverse reactions were evaluated with FORXIGA 10 mg versus placebo in a dedicated CV outcomes trial (DECLARE-TIMI 58).

*Placebo-Controlled Studies for FORXIGA 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 FORXIGA was used as monotherapy, and in 8 studies FORXIGA was used as add-on to background antidiabetic therapy or as combination therapy with metformin. These data reflect exposure of 2338 patients to FORXIGA with a mean exposure duration of 21 weeks. Patients received placebo (N=1393), FORXIGA 5 mg (N=1145), or FORXIGA 10 mg (N=1193) once daily.

*Pool of 13 Placebo-Controlled Studies for FORXIGA 10 mg:* The safety and tolerability of FORXIGA 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 FORXIGA 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 FORXIGA and 3403 were treated with control (either as monotherapy or in combination with other antidiabetic therapies).

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

The adverse events in the 12-study placebo-controlled pooled analysis reported in  $\geq 2\%$  of T2DM patients treated with FORXIGA 5 mg or 10 mg for glycemic control, and occurring more frequently than in patients treated with placebo, are shown in Table 1.

**Table 1**                      **Adverse Events Reported in  $\geq 2\%$  of T2DM Patients Treated for Glycemic Control with FORXIGA 5 mg or 10 mg and More Frequently than in Patients Treated with Placebo**

System organ class Preferred term	% of Patients (Pool of 12 Placebo-controlled Studies)		
	FORXIGA 5 mg N=1145	FORXIGA 10 mg N=1193	Placebo N=1393
<b>Gastrointestinal disorders</b>			
Constipation	2.2	1.9	1.5
Nausea	2.8	2.5	2.4
<b>Infections and infestations</b>			
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
<b>Metabolism and nutrition disorders</b>			
Dyslipidemia	2.1	2.5	1.5
<b>Musculoskeletal and Connective Tissue Disorders</b>			
Back pain	3.1	4.2	3.2
Pain in extremity	2.0	1.7	1.4
<b>Renal and Urinary disorders</b>			
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: FORXIGA 5 mg=581, FORXIGA 10 mg=598, Placebo=677).

‡ Genital mycotic infections include the following preferred terms, listed in order of frequency reported for males: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection male, penile infection, balanoposthitis, balanoposthitis infective, genital infection and posthitis (N for males: FORXIGA 5 mg=564, FORXIGA 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 T2DM patients, treated with FORXIGA for glycemic control, seen more frequently than in patients in the placebo/comparator group, and reported in at least three or more patients treated with FORXIGA 5 mg or 10 mg are described below by treatment regimen.

**Table 2** Adverse Events Reported in  $\geq 5\%$  of T2DM Patients Treated with FORXIGA 5 mg or 10 mg for Glycemic Control and Observed More Frequently than in Patients Treated with Placebo/Comparator and Reported in at least Three or More Patients Treated with FORXIGA 5 mg or 10 mg

Treatment Regimen Adverse Event (Preferred term)	n (%) of Patients		
	FORXIGA 5 mg	FORXIGA 10 mg	Placebo/ Comparator
<b>Monotherapy</b>	<b>N=132</b>	<b>N=146</b>	<b>N=75</b>
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)
<b>Add-on to Metformin</b>	<b>N=137</b>	<b>N=135</b>	<b>N=137</b>
Diarrhea	5 (3.6)	10 (7.4)	7 (5.1)
Headache	10 (7.3)	11 (8.1)	6 (4.4)
<b>Add-on to Metformin versus Glipizide</b>	<b>FORXIGA (any dose)</b>		<b>N=408</b>
	<b>N=406</b>		
Headache	21 (5.2)		17 (4.2)

### **Less Common Clinical Trial Adverse Drug Reactions in Patients with T2DM Being Treated for Glycemic Control (<2 %)<sup>1</sup>**

**Gastrointestinal disorder:** dry mouth.

**Investigations:** weight decreased.

<sup>1</sup> 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.

**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 in T2DM Patients Being Treated for Glycemic Control**

**Volume depletion and hypotension:** Events related to volume depletion (including reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension) were reported in 0.6%, 0.8% and 0.4% of patients who received FORXIGA 5 mg, FORXIGA 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 FORXIGA 10 mg and comparator.

Postural blood pressure measurement revealed orthostatic hypotension in 13.1% of patients treated with FORXIGA 10 mg vs. 11.3% of patients treated with placebo over the 24-week treatment period. In addition, in two studies with patients with T2DM and hypertension, postural blood pressure measurement revealed orthostatic hypotension in 3.2% of FORXIGA 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 FORXIGA 5 mg, FORXIGA 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] FORXIGA 5 mg and 10 mg, respectively, vs. 1.5% [10/677] placebo) than in males (2.8% [16/564], 2.7% [16/595] FORXIGA 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 1).

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 FORXIGA 5 mg, FORXIGA 10 mg and placebo, respectively).

**Urinary tract infections:** Events of urinary tract infections (UTI) were reported in 5.7% (65/1145), 4.3% (51/1193), and 3.7% (52/1393) of patients who received FORXIGA 5 mg, FORXIGA 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] FORXIGA 5 mg and 10 mg, respectively, vs. 6.6% [45/677] placebo) than in males (1.6% [9/564] and 0.8% [5/595] FORXIGA 5 mg and 10 mg, respectively, vs. 1.0% [7/716] placebo).

In 9 of the 13 studies in the FORXIGA 10 mg placebo-controlled pool for which long-term treatment data were available (mean duration of treatment 439.5 days for FORXIGA 10 mg

and 419.0 days for placebo), of the 174 patients treated with FORXIGA 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 FORXIGA 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 FORXIGA 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 3). Studies of FORXIGA as an add-on to sulfonylurea or as an add-on to insulin therapy had higher rates of hypoglycemia with FORXIGA treatment than with placebo treatment (see WARNINGS AND PRECAUTIONS).

**Table 3 Incidence of Major\* and Minor† Hypoglycemia in Placebo-Controlled Studies in T2DM Patients Being Treated for Glycemic Control**

	FORXIGA 5 mg	FORXIGA 10 mg	Placebo
<b>Monotherapy (24 weeks)</b>	N=64	N=70	N=75
Major [n (%)]	0	0	0
Minor [n (%)]	0	0	0
<b>Add-on to Metformin (24 weeks)</b>	N=137	N=135	N=137
Major [n (%)]	0	0	0
Minor [n (%)]	2 (1.5)	1 (0.7)	0
<b>Active Control Add-on to Metformin vs. Glipizide (52 weeks)</b>	-	N=406	N=408
Major [n (%)]	-	0	3 (0.7)
Minor [n (%)]	-	7 (1.7)	147 (36.0)
<b>Add-on to Glimepiride (24 weeks)</b>	N=145	N=151	N=146
Major [n (%)]	0	0	0
Minor [n (%)]	8 (5.5)	9 (6.0)	3 (2.1)
<b>Add-on to Metformin and Sulfonylurea (24 weeks)</b>	-	N=109	N=109
Major [n (%)]	-	0	0
Minor [n (%)]	-	14 (12.8)	4 (3.7)
<b>Add-on to Sitagliptin alone or with metformin (24 weeks)</b>	-	N=225	N=226
Major [n (%)]	-	1 (0.4)	0

**Table 3 Incidence of Major\* and Minor† Hypoglycemia in Placebo-Controlled Studies in T2DM Patients Being Treated for Glycemic Control**

	FORXIGA 5 mg	FORXIGA 10 mg	Placebo
Minor [n (%)]	-	4 (1.8)	3 (1.3)
<b>Add-on to Insulin with or without other OADs (24 weeks)</b>	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)
<b>CV outcomes study (42 months mean exposure) §</b>			
<b>All Patients</b>	-	N=8574	N=8569
Major [n (%)]	-	58 (0.7)	83 (1.0)
Minor [n (%)]	-	Not collected	Not collected
<b>Patients treated with Insulin</b>	-	N=4177	N=4606
Major [n (%)]	-	52 (1.2)	64 (1.4)
<b>Patients treated with a Sulfonylurea</b>	-	N=4118	N=4521
Major [n(%)]	-	14 (0.3)	23 (0.5)

\* Major episodes of hypoglycemia were defined as symptomatic episodes requiring external (third party) assistance due to severe impairment in consciousness or 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

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

**Monotherapy and add-on to metformin:** In studies with FORXIGA used as monotherapy, add-on to metformin, and initial combination with metformin for up to 102 weeks, 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 FORXIGA 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 FORXIGA plus metformin. Minor episodes of hypoglycemia were reported in 2.5% of patients treated with FORXIGA plus metformin and 42.4% of patients treated with glipizide plus metformin.

**Add-on to sulfonylureas:** In a study with FORXIGA added on to glimepiride for up to 48 weeks there was one episode of major hypoglycemia reported in a patient treated with dapagliflozin 2.5 mg plus glimepiride. Minor episodes of hypoglycemia were reported in 8.3%



and 7.9% of patients treated with FORXIGA 5 mg and 10 mg plus glimepiride, respectively, and 2.1% of patients treated with placebo plus glimepiride.

**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 FORXIGA 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 FORXIGA 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 FORXIGA 10 mg plus sitagliptin (without metformin). Minor episodes of hypoglycemia were reported in 2.2% and 1.3% of patients treated with FORXIGA 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 FORXIGA 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 FORXIGA 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 FORXIGA 10 mg compared with those treated with placebo.

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

**Patients with renal impairment:** Safety was also assessed in two dedicated studies of T2DM patients being treated for glycemic control, with moderate renal impairment ( $\text{eGFR} \geq 45$  to  $< 60$  mL/min/1.73m<sup>2</sup> and  $\text{eGFR} \geq 30$  to  $< 60$  mL/min/1.73m<sup>2</sup>, respectively).

In the study of patients with  $\text{eGFR} \geq 45$  to  $< 60$  mL/min/1.73m<sup>2</sup>, at Week 24, FORXIGA was associated with changes in mean eGFR (FORXIGA: -3.39 mL/min/1.73m<sup>2</sup> and placebo: -0.90 mL/min/1.73m<sup>2</sup>). The mean eGFR in the dapagliflozin group decreased initially (during the first 4 weeks of treatment) and remained steady for the remaining 20 weeks of treatment. At 3 weeks after termination of FORXIGA, the mean change from baseline in eGFR in the dapagliflozin group was similar to the mean change in the placebo group (FORXIGA: 0.57 mL/min/1.73m<sup>2</sup> and placebo: -0.04 mL/min/1.73m<sup>2</sup>). A higher proportion of subjects treated with dapagliflozin had adverse reactions of hypotension, compared with placebo.

In the study of patients with eGFR  $\geq 30$  to  $< 60$  mL/min/1.73m<sup>2</sup>, at Week 52, FORXIGA was associated with changes from baseline in mean eGFR (eGFR: FORXIGA 5 mg: -2.08 mL/min/1.73m<sup>2</sup>, FORXIGA 10 mg -4.46 mL/min/1.73m<sup>2</sup> and placebo -2.58 mL/min/1.73m<sup>2</sup>). At Week 104, these changes persisted (eGFR: FORXIGA 5 mg -1.71 mL/min/1.73m<sup>2</sup>, FORXIGA 10 mg -3.50 mL/min/1.73m<sup>2</sup> and placebo -2.38 mL/min/1.73m<sup>2</sup>). With FORXIGA 5 mg and 10 mg, these eGFR reductions were evident at Week 1 while placebo treated patients had a slow continuous decline through Week 104.

**Diabetic ketoacidosis in patients with diabetes:** Cases of DKA, a serious life-threatening condition requiring urgent hospitalization, have been reported in patients with T2DM treated with FORXIGA and other SGLT2 inhibitors. Some cases of DKA have been fatal. FORXIGA 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).

#### **Cardiovascular Outcomes Study (DECLARE-TIMI 58)**

DECLARE-TIMI 58 evaluated the safety and tolerability of FORXIGA 10 mg (n=8574) versus placebo (n=8569) in adult patients with T2DM and CV risk factors or established cardiovascular disease. The mean exposure time was 42 months. In total, there were 30623 patient-years of exposure to FORXIGA. The safety variables collected in DECLARE-TIMI 58 included: serious adverse events (SAE), adverse events leading to discontinuation of study drug (DAE), CV events, amputation events, DKA events, and adverse events of special interest. Adverse events of special interest consisted of: malignancies, hepatic events, major hypoglycemic events, fractures, renal events, symptoms of volume depletion, hypersensitivity reactions, urinary tract infections, and genital infections.

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

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

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

Adjudicated events of DKA were reported in 27 patients (0.3%) in the FORXIGA 10 mg group and 12 patients (0.1%) in the placebo groups (0.04 and 0.09 events per 100 patient-years, respectively). The events were evenly distributed throughout the study period. Of the 27 patients with DKA events in the FORXIGA group, 22 had concomitant insulin treatment at the time of the event.

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

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

Events of fractures occurred in 7.4% and 5.8% of patients  $\geq 75$  years of age in the FORXIGA and placebo groups, respectively.

#### **Abnormal Hematologic and Clinical Chemistry Findings in T2DM Patients Being Treated for Glycemic Control**

*Increases in serum creatinine, blood urea nitrogen (BUN) and decreased eGFR:* In the pool of 13 placebo-controlled studies, in FORXIGA-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 4 Mean Changes from Baseline for Serum Creatinine and eGFR at Week 1 and Week 24**

Study Week/ Treatment Group	Week 1*		Week 24*	
	FORXIGA 10 mg	Placebo	FORXIGA 10 mg	Placebo
<b>Serum creatinine, <math>\mu\text{mol/L}</math> (mg/dL)</b>				
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
<b>eGFR, mL/min/1.73m<sup>2</sup></b>				
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 in patients with T2DM being treated for glycemic control

*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 FORXIGA-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 5 Mean Changes from Baseline for Hemoglobin and Hematocrit at Week 24 and Week 102**

Study Week/ Treatment Group	Week 24*		Week 102**	
	FORXIGA 10 mg	Placebo	FORXIGA 10 mg	Placebo
<b>Hemoglobin, g/L (g/dL)</b>				
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
<b>Hematocrit, %</b>				
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 in patients with T2DM being treated for glycemic control

\*\*Pool of 9 placebo-controlled studies in patients with T2DM being treated for glycemic control

By Week 24, hematocrit values >55% were reported in 1.3% of FORXIGA 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 FORXIGA 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 FORXIGA 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 6 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**	
	FORXIGA 10 mg	Placebo	FORXIGA 10 mg	Placebo
<b>Serum Inorganic Phosphorus, µmol/L (mg/dL)</b>				

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
<b>Hyperphosphatemia<sup>†</sup></b>				
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 in patients with T2DM being treated for glycemic control

\*\*Pool of 9 placebo-controlled studies in patients with T2DM being treated for glycemic control

<sup>†</sup>Defined as  $\geq 1.81$  mmol/L ( $\geq 5.6$  mg/dL) if age 17 - 65 or  $\geq 1.65$  mmol/L ( $\geq 5.1$  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 FORXIGA 10 mg-treated patients compared with placebo-treated patients (see below).

**Table 7 Mean Changes from Baseline for Lipid Parameters at Week 24 and Week 102**

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

\*Pool of 13 placebo-controlled studies in patients with T2DM being treated for glycemic control

\*\*Pool of 9 placebo-controlled studies in patients with T2DM being treated for glycemic control

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

### **Clinical Trial in Patients with Heart Failure (DAPA-HF)**

The DAPA-HF study (see CLINICAL TRIALS) was a dedicated CV outcomes study in adult patients with HFrEF which assessed the safety and tolerability of FORXIGA 10 mg, as add-on to standard of care therapy for heart failure. These data reflect exposure of 2368 patients to

FORXIGA 10 mg and a median exposure time of 18 months. In total, there were 3310 patient-years of exposure to FORXIGA.

The DAPA-HF study included 1926 (41%) patients with eGFR below 60 mL/min/1.73m<sup>2</sup> and 719 (15%) with eGFR below 45 mL/min/1.73m<sup>2</sup>. No overall differences in safety were seen in these patients compared to patients with normal renal function.

There were 2714 (57%) out of 4744 patients older than 65 years with HFrEF included in the DAPA-HF study. Safety was similar for patients age 65 years and younger and those older than 65. There was no increased risk in events of volume depletion or acute kidney injury.

The number of patients with events related to volume depletion (including reports of hypotension, hypovolemia, dehydration, or orthostatic hypotension) were 170 (7.2%) and 153 (6.5%) in the FORXIGA-treated and placebo groups, respectively. Serious events of symptoms suggestive of volume depletion were reported in 23 (1.0%) patients in the FORXIGA-treated group and in 38 (1.6%) patients in the placebo group.

The number of patients with renal adverse events were 141 (6.0%) and 158 (6.7%) in the FORXIGA-treated and the placebo group, respectively. Serious renal adverse events were reported in (1.4%) patients in the FORXIGA-treated group and 58 (2.4%) patients in the placebo group.

Severe hypoglycemia and DKA events were observed only in patients with T2DM. The number of patients with severe hypoglycemia events were 4 (0.2%) in the FORXIGA-treated and 4 (0.2%) in the placebo group. The number of patients with DKA events were 3 (0.1%) in the FORXIGA-treated group and none in the placebo group.

There were no patients with serious events of genital infections in the FORXIGA-treated group and one in the placebo group. There were 7 (0.3%) patients with adverse events leading to discontinuations of study treatment due to genital infections in the FORXIGA-treated group and none in the placebo group.

There were 14 (0.6%) patients with serious events of urinary tract infections in the FORXIGA-treated group and 17 (0.7%) patients in the placebo group. There were 5 (0.2%) patients with adverse events leading to discontinuations of study treatment due to urinary tract infections in the FORXIGA-treated group and 5 (0.2%) patients in the placebo group.

### **Post-Market Adverse Drug Reactions**

The following adverse reactions have been identified during post-approval use of FORXIGA in patients with T2DM. 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.

**Genitourinary:** severe urinary tract infections; urosepsis and pyelonephritis

**Hepatic/Biliary/Pancreatic:** acute pancreatitis

**Infection and Infestations:** necrotizing fasciitis of the perineum (Fournier's gangrene) (see (WARNINGS AND PRECAUTIONS, Genitourinary)

**Metabolism:** 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 macular-papular, rash pustular and rash vesicular)

## DRUG INTERACTIONS

### Overview

#### In vitro assessment of interactions

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.

### Drug-Drug Interactions

#### Pharmacokinetic interactions

*Effect of other drugs on dapagliflozin:* In studies conducted in healthy subjects, the pharmacokinetics of dapagliflozin were not altered by the coadministered drugs (see Table 8).

**Table 8** 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
		Cmax	AUC <sup>†</sup>	
Oral Antidiabetic Agents				
Metformin (1000 mg)	20 mg	0.932 (0.848, 1.024)	0.995 (0.945, 1.053)	No dosing adjustment required
Pioglitazone (45 mg)	50 mg	1.09 (1.00, 1.18)	1.03 (0.98, 1.08)	No dosing adjustment required

**Table 8** 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 <sub>max</sub>	AUC <sup>†</sup>	
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
<b>Other Medications</b>				
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
<b>Anti-infective Agent</b>				
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.

<sup>†</sup> 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).



*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 9).

**Table 9 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
		Cmax	AUC†	
Oral Antidiabetic Agents				
Metformin (1000 mg)	20 mg	0.953 (0.866, 1.049)	1.001 (0.933, 1.075)	No dosing adjustment required
Pioglitazone (45 mg)	50 mg	0.93 (0.75, 1.15)	1.00 (0.90, 1.13)	No dosing adjustment required
Sitagliptin (100 mg)	20 mg	0.887 (0.807, 0.974)	1.012 (0.985, 1.040)	No dosing adjustment required
Glimepiride (4 mg)	20 mg	1.043 (0.905, 1.201)	1.132 (0.996, 1.287)	No dosing adjustment required
Other Medications				
Hydrochlorothiazide (25 mg)	50 mg	NC	0.99 (0.95, 1.04)	No dosing adjustment required
Bumetanide (1 mg)**	10 mg once daily for 7 days	1.132 (0.979, 1.310)	1.132 (0.985, 1.302)	No dosing adjustment required
Valsartan (320 mg)	20 mg	0.938 (0.762, 1.156)	1.046 (0.850, 1.286)	No dosing adjustment required
Simvastatin (40 mg)	20 mg	0.936 (0.816, 1.073)	1.193 (1.018, 1.399)	No dosing adjustment required
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	S-warfarin		No dosing

**Table 9 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 <sub>max</sub>	AUC <sup>†</sup>	
	10 mg once daily for 7 days	1.030 (0.994, 1.124)	1.068 (1.002, 1.138)	adjustment required
		R-warfarin		
		1.057 (0.977, 1.145)	1.079 (1.030, 1.130)	

\* Single dose unless otherwise noted.

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

<sup>†</sup> 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]).

### Pharmacodynamic interactions

*Diuretics:* FORXIGA may add to the diuretic effect of loop diuretics and may increase the risk of dehydration and hypotension (see WARNINGS AND PRECAUTIONS).

### Drug-Food Interactions

Interactions with food have not been studied (see DOSAGE AND ADMINISTRATION, Dosing Considerations).

### Drug-Herb Interactions

The effects of herbal products on the pharmacokinetics of dapagliflozin have not been studied.

### Drug-Laboratory Interactions

Due to its mechanism of action, patients taking FORXIGA will test positive for glucose in their urine. Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

### Drug-Lifestyle Interactions

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

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 FORXIGA is used as add-on therapy with insulin or an insulin secretagogue.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

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

### **Recommended Dose and Dosage Adjustment**

#### **Type 2 Diabetes Mellitus**

To improve glycemic control, the recommended starting dose of FORXIGA is 5 mg taken once daily at any time of the day with or without food. In patients tolerating FORXIGA 5 mg once daily and who require additional glycemic control, the dose can be increased to 10 mg daily.

To reduce the risk of hospitalization due to HF, the recommended dose of FORXIGA is 10 mg once daily.

In patients with evidence of volume depletion, this condition should be corrected prior to initiation of FORXIGA (see WARNINGS AND PRECAUTIONS).

#### **Heart Failure (DAPA-HF)**

To reduce the risk of CV death, hospitalization for HF and urgent HF visit in patients with HFrEF, the recommended dose of FORXIGA is 10 mg taken orally once daily at any time of the day regardless of meals.

In the DAPA-HF study, FORXIGA was used in conjunction with other heart failure therapies.

#### **Renal impairment:**

##### ***Type 2 Diabetes Mellitus***

The glycemic efficacy of FORXIGA is dependent on renal function and declines with decreasing renal function. Renal function should be assessed prior to initiation of FORXIGA therapy and periodically thereafter, with more intensive monitoring of glycemic and renal biomarkers, and signs and symptoms of renal dysfunction in patients whose eGFR decreases  $<60 \text{ mL/min/1.73m}^2$ . No dosage adjustment for FORXIGA is required in T2DM patients, who

are being treated for glycemic control, with mild to moderate (CKD 3A) renal impairment (eGFR  $\geq 45$  mL/min/1.73m<sup>2</sup>).

FORXIGA is not recommended for use in patients with T2DM, being treated for glycemic control, with an eGFR persistently  $< 45$  mL/min/1.73m<sup>2</sup>, severe renal impairment, ESRD, or patients on dialysis as the glycemic efficacy of dapagliflozin is dependent on renal function (see ADVERSE REACTIONS and CLINICAL TRIALS). FORXIGA is contraindicated in patients with an eGFR less than 30 mL/min/1.73m<sup>2</sup>, end-stage renal disease (ESRD) or patients on dialysis (see CONTRAINDICATIONS).

### ***Heart Failure (DAPA-HF)***

No dosage adjustment is required based on renal function. FORXIGA is contraindicated in patients with an eGFR less than 30 mL/min/1.73m<sup>2</sup>, end-stage renal disease (ESRD) or patients on dialysis (see CONTRAINDICATIONS).

**Hepatic impairment:** No dosage adjustment for FORXIGA is necessary for patients with mild or moderate hepatic impairment. FORXIGA exposure is increased in patients with severe hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics). Therefore, FORXIGA is not recommended for use in this population.

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

**Geriatrics ( $\geq 65$  years of age):** No dosage adjustment for FORXIGA is required based on age; however renal function and risk of volume depletion should be taken into account (see WARNINGS AND PRECAUTIONS).

### **Missed Dose**

If a dose of FORXIGA is missed, it should be taken as soon as the patient remembers. A double dose of FORXIGA should not be taken on the same day.

## **OVERDOSAGE**

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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.
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## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

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

### **Type 2 Diabetes Mellitus**

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.

### **Heart Failure (DAPA-HF)**

Dapagliflozin increases the delivery of sodium to the distal tubule which is believed to increase tubuloglomerular feedback and reduce intraglomerular pressure. Secondary effects of SGLT2 inhibition with dapagliflozin also include a modest reduction in blood pressure, reduction in body weight, and an increase in hematocrit.

The cardiovascular benefits of dapagliflozin are not solely dependent on the blood glucose-lowering effect and not limited to patients with diabetes.

### **Pharmacodynamics**

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients with T2DM following the administration of dapagliflozin. Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day) at a dapagliflozin dose of 10 mg/day in patients with T2DM for 12 weeks. This glucose elimination rate approached the maximum glucose excretion observed at 20 mg/day of dapagliflozin. Evidence of sustained glucose excretion was seen in patients with T2DM given dapagliflozin 10 mg/day for up to 2 years.

This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume. Urinary volume increases in patients with T2DM treated with FORXIGA 10 mg were sustained at 12 weeks and amounted to approximately 375 mL/day. The increase in urinary volume was associated with a small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations.

Urinary uric acid excretion was also increased transiently (for 3-7 days) and accompanied by a reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations ranged from 18.3 to 48.3  $\mu\text{mol/L}$  (0.33 mg/dL to 0.87 mg/dL).

**N-terminal pro-B-type natriuretic peptide (NT-proBNP):** In the DAPA-HF study (see CLINICAL TRIALS), the mean change from baseline for NT-proBNP at 8 months was -196 pg/mL in the FORXIGA-treated group and 101 pg/mL in the placebo group.

**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**

**Absorption:** Dapagliflozin was rapidly and well absorbed after oral administration and can be administered with or without food. Geometric mean steady-state dapagliflozin C<sub>max</sub> and AUC<sub>τ</sub> values following once daily 10 mg doses of dapagliflozin were 158 ng/mL and 628 ng.h/mL, respectively. Maximum dapagliflozin plasma concentrations (C<sub>max</sub>) were usually attained within 2 hours after administration in the fasted state. The C<sub>max</sub> 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<sub>max</sub> by up to 50% and prolonged T<sub>max</sub> by approximately 1 hour, but did not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful.

**Distribution:** Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (e.g., renal or hepatic impairment).

**Metabolism:** 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<sub>1/2</sub>) for dapagliflozin was 12.9 hours following a single oral dose of FORXIGA 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 [<sup>14</sup>C]-dapagliflozin dose and was the predominant drug-related component in human plasma, accounting for 42% (based on AUC<sub>[0-12 h]</sub>) 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.

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

### **Special Populations and Conditions**

**Pediatrics (<18 years of age):** Pharmacokinetics in the pediatric and adolescent population have not been studied.

**Age:** No dosage adjustment for dapagliflozin is recommended on the basis of age. The effect of age (young:  $\geq 18$  to  $< 40$  years [ $n=105$ ] and elderly:  $\geq 65$  years [ $n=224$ ]) was evaluated as a covariate in a population pharmacokinetic model and compared to patients  $\geq 40$  to  $< 65$  years using data from healthy subject and T2DM 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.

**Gender:** No dosage adjustment is recommended for dapagliflozin on the basis of gender. Gender was evaluated as a covariate in a population pharmacokinetic model using data from healthy subject and T2DM patient studies. The mean dapagliflozin AUC<sub>ss</sub> in females ( $n=619$ ) was estimated to be 22% higher than in males ( $n=634$ ) (90% CI: 117, 124).

**Race:** No dosage adjustment 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 T2DM 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).

**Body weight:** No dose adjustment is recommended on the basis of weight. In a population pharmacokinetic analysis using data from healthy subject and T2DM patient studies, systemic exposures in high body weight subjects ( $\geq 120$  kg,  $n=91$ ) were estimated to be 78.3% (90% CI: 78.2, 83.2%) of those of reference subjects with body weight between 75 and 100 kg. No dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in T2DM patients with high body weight ( $\geq 120$  kg) is recommended. Subjects with low body weights ( $< 50$  kg) were not well represented in the healthy subject and patient studies used in the population pharmacokinetic analysis. Therefore, dapagliflozin systemic exposures were simulated with a large number of subjects. The simulated mean dapagliflozin systemic exposures in low body weight subjects were estimated to be 29% higher than subjects with the reference group body

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

**Renal impairment:** FORXIGA is not recommended for use in patients with T2DM, being treated for glycemic control, with an eGFR persistently <45 mL/min/1.73m<sup>2</sup>, severe renal impairment, ESRD, or patients on dialysis as the glycemic efficacy of dapagliflozin is dependent on renal function (see WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, and CLINICAL TRIALS). FORXIGA is contraindicated in patients with an eGFR less than 30 mL/min/1.73m<sup>2</sup>, ESRD or patients on dialysis (see CONTRAINDICATIONS).

At steady-state (20 mg once-daily dapagliflozin for 7 days), patients with T2DM and mild, moderate or severe renal impairment (as determined by iohexol clearance) had mean systemic exposures of dapagliflozin that were 32%, 60% and 87% higher, respectively, than those of patients with T2DM and normal renal function. Higher systemic exposures to dapagliflozin in patients with T2DM and renal impairment did not result in a correspondingly higher renal glucose clearance or total cumulative glucose excretion. The renal glucose clearance and 24-hour glucose excretion were lower in patients with moderate or severe renal impairment as compared to patients with normal and mild renal impairment. The steady-state 24-hour urinary glucose excretion was highly dependent on renal function and 85, 52, 18 and 11 g of glucose/day was excreted by patients with T2DM and normal renal function or mild, moderate or severe renal impairment, respectively. There were no differences in the protein binding of dapagliflozin between renal impairment groups or compared to healthy subjects. The impact of hemodialysis on dapagliflozin exposure is not known.

**Hepatic impairment:** 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<sub>max</sub> and AUC of dapagliflozin were up to 12% and 36% higher, respectively, compared to healthy matched control subjects. No dose adjustment from the proposed usual dose of dapagliflozin is proposed for these populations. In patients with severe hepatic impairment (Child-Pugh class C) mean C<sub>max</sub> and AUC of dapagliflozin were up to 40% and 67% higher than matched healthy controls, respectively.

## STORAGE AND STABILITY

Store at room temperature (15-30°C).

## SPECIAL HANDLING INSTRUCTIONS

Store in a safe place and out of the reach of children.



## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

### **Dosage Forms and Packaging**

FORXIGA 5 mg tablets are yellow, biconvex, round, film coated tablets with “5” engraved on one side and “1427” engraved on the other side.

FORXIGA (dapagliflozin) 10 mg tablets are yellow, biconvex, diamond, film coated tablets with “10” engraved on one side and “1428” engraved on the other side.

The 5 mg and 10 mg tablets are provided in blisters in cartons of 30.

Information for the patient is provided as a package insert in the FORXIGA packages.

### **Composition**

FORXIGA is available as a film-coated tablet for oral administration containing the equivalent of 5 mg or 10 mg dapagliflozin as dapagliflozin propanediol monohydrate.

Each film-coated tablet of FORXIGA also contains the following inactive ingredients: anhydrous lactose, crospovidone, magnesium stearate, microcrystalline cellulose, silicon dioxide. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc and yellow iron oxide.

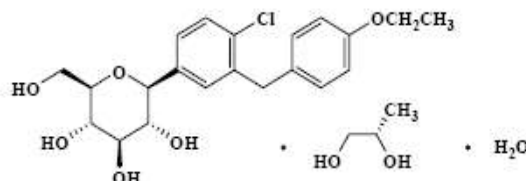
## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

<b>Common Name:</b>	dapagliflozin propanediol monohydrate
<b>Chemical Name:</b>	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)
<b>Molecular Formula and Molecular Mass:</b>	$C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$ 502.98; 408.87 (dapagliflozin)

#### Structural Formula:



<b>Physicochemical Properties:</b>	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.
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### CLINICAL TRIALS

#### Clinical Trials in Patients with T2DM Treated for Glycemic Control

FORXIGA (dapagliflozin) was studied as monotherapy and in combination with other antidiabetic medications, including metformin, glimepiride, or insulin. FORXIGA was also studied in patients with T2DM and CV disease and in patients with mild to moderate renal impairment.

Treatment with FORXIGA as monotherapy and in combination with metformin, glimepiride, or 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 postprandial glucose (PPG) (where measured), compared to placebo or control. The estimated, placebo-adjusted, HbA1c reduction across trials and doses ranged from 0.40% to 0.84%. These glycemic effects were sustained in long-term extensions up to 104 weeks. HbA1c reductions were seen across subgroups including gender, age, race, duration of disease, and

baseline body mass index (BMI). In addition, patients treated with FORXIGA compared to placebo or control achieved greater HbA1c reductions in patients with a baseline HbA1c  $\geq 9\%$ .

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

### Clinical Trial in Patients with Heart Failure (DAPA-HF)

The effect of FORXIGA 10 mg once daily versus placebo, on top of standard of care, on CV death, hospitalization for heart failure (HF) and urgent HF visits in patients with HFrEF (New York Heart Association [NYHA] II-IV) was assessed in a Phase III study. FORXIGA demonstrated a statistically significant reduction in the incidence of the primary composite endpoint of CV death, hospitalization for heart failure or urgent heart failure visit compared with placebo, with all three components individually contributing to the treatment effect.

### Study demographics and trial design

**Table 10** Summary of patient demographics for clinical trials in specific indications

Study #	Trial design	Dosage, route of administration and duration	N per group/ N treated with dapagliflozin/ Total	Mean age	Gender (% M/F)
<b>Clinical Trials in Patients with T2DM Treated for Glycemic Control</b>					
<b>Monotherapy</b>					
1	Multicentre, randomized, double-blind, placebo-controlled	<p><u>Group 1:</u> dapagliflozin 2.5, 5 or 10 mg, QAM or QPM, vs. placebo Oral, 24 weeks + 78 weeks</p> <p><u>Group 2:</u> dapagliflozin 5 or 10 mg, QAM Oral, 24 weeks + 78 weeks</p>	<p>64 - 76/ 410/ 485 (ST)</p> <p>34, 39/ 73/ 73 (ST)</p>	<p>52.6</p> <p>48.1</p>	<p>47/53</p> <p>64/36</p>
<b>Add-on Combination Therapy with Metformin</b>					
2	Multicentre, randomized, double-blind, placebo-controlled	<p>4 groups: dapagliflozin 2.5, 5, or 10 mg or placebo Background therapy: metformin <math>\geq 1500</math> mg/day Oral, 24 weeks + 78 weeks</p>	<p>135 - 137/ 409/ 546 (ST)</p>	53.9	53/47

Study #	Trial design	Dosage, route of administration and duration	N per group/ N treated with dapagliflozin/ Total	Mean age	Gender (% M/F)
3	Multicentre, randomized, double-blind, active-controlled	2 groups: dapagliflozin titrated dose of 2.5, 5, or 10 mg or glipizide titrated dose of 5, 10, or 20 mg Background therapy: metformin $\geq 1500$ mg Oral, 52 weeks + 52 weeks + 52 weeks	406 - 408/ 406/ 814 (ST)	58.4	55/45
<b>Add-on Combination Therapy with a Sulfonylurea</b>					
4	Multicentre, randomized, double-blind, placebo-controlled	4 groups: dapagliflozin 2.5, 5, or 10 mg or placebo Background therapy: glimepiride 4 mg/day Oral, 24 weeks + 24 weeks	146 - 154/ 450/ 596 (ST)	59.8	48/52
<b>Add-on Combination Therapy with Metformin and a Sulfonylurea</b>					
5	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
<b>Add-on Combination Therapy with Sitagliptin Alone or with Metformin</b>					
6	Multicentre, randomized, double-blind, placebo-controlled	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
<b>Add-on Combination Therapy with Insulin</b>					
7	Multicentre, randomized, double-blind, placebo-controlled	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
<b>Cardiovascular Outcomes in Patients with T2DM</b>					

Study #	Trial design	Dosage, route of administration and duration	N per group/ N treated with dapagliflozin/ Total	Mean age	Gender (% M/F)
8	Multicentre, randomized, double-blind, placebo-controlled	2 groups: dapagliflozin 10 mg or placebo Oral, mean follow-up time of 4.1 years	8578-8582/ 8582/ 17160	63.9	63/37
<b>Clinical Trial in Patients with Heart Failure</b>					
9	Multicentre, randomized, double-blind, placebo-controlled	Dapagliflozin 10 mg or placebo	2373 – 2371/ 2368/ 4744	66	77/23

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

## Study results

### Clinical Trials in Patients with T2DM Treated for Glycemic Control

#### *Monotherapy (Study 1)*

The efficacy and safety of FORXIGA as monotherapy was evaluated in a double-blind, placebo-controlled study of 24 weeks duration in treatment-naïve patients. Following a 2-week diet and exercise placebo lead-in period, 485 patients with HbA1c  $\geq 7\%$  and  $\leq 10\%$  were randomized to dapagliflozin 2.5 mg, FORXIGA 5 mg, or 10 mg once daily in either the morning (QAM, main cohort) or evening (QPM), or placebo in the morning only.

As shown in Table 11, statistically significant reductions ( $p < 0.001$ ) in HbA1c and FPG relative to placebo were observed with FORXIGA 5 mg and 10 mg QAM at Week 24 which were sustained long term. Overall, the PM administration of FORXIGA had a comparable safety and efficacy profile to FORXIGA administered in the AM.

**Table 11 Results at Week 24 (LOCF\*) in a Placebo-Controlled Study of FORXIGA Monotherapy in Patients with Type 2 Diabetes (Main Cohort AM Doses)**

Efficacy Parameter	FORXIGA 5 mg N=64 <sup>†</sup>	FORXIGA 10 mg N=70 <sup>†</sup>	Placebo N=75 <sup>†</sup>
<b>HbA1c (%)</b>			
Baseline (mean)	7.83	8.01	7.79
Change from baseline (adjusted mean <sup>‡</sup> )	-0.77	-0.89	-0.23
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-0.54 <sup>§</sup> (-0.84, -0.24)	-0.66 <sup>§</sup> (-0.96, -0.36)	
Patients (%) achieving HbA1c <7% adjusted for baseline	44.2 <sup>¶</sup>	50.8 <sup>¶</sup>	31.6

**Table 11 Results at Week 24 (LOCF<sup>\*</sup>) in a Placebo-Controlled Study of FORXIGA Monotherapy in Patients with Type 2 Diabetes (Main Cohort AM Doses)**

<b>Efficacy Parameter</b>	<b>FORXIGA 5 mg N=64<sup>†</sup></b>	<b>FORXIGA 10 mg N=70<sup>†</sup></b>	<b>Placebo N=75<sup>†</sup></b>
<b>FPG (mmol/L)</b>			
Baseline (mean)	8.7	9.3	8.9
Change from baseline (adjusted mean <sup>‡</sup> )	-1.3	-1.6	-0.2
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-1.1 <sup>§</sup> (-1.7, -0.5)	-1.4 <sup>§</sup> (-2.0, -0.8)	
<b>Body Weight (kg)</b>			
Baseline (mean)	87.17	94.13	88.77
Change from baseline (adjusted mean <sup>‡</sup> )	-2.83	-3.16	-2.19
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-0.65 (-1.90, 0.61)	-0.97 (-2.20, 0.25)	

\* 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 <0.001 vs. placebo.

¶ Not evaluated for statistical significance as a result of the sequential testing procedure for the secondary endpoints

## Combination Therapy

### *Add-On Therapy with Metformin (Study 2)*

A 24-week double-blind, placebo-controlled study was conducted to evaluate FORXIGA in combination with metformin in patients with T2DM 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, FORXIGA 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 FORXIGA 5 mg and 10 mg at Week 24 which were sustained long term.

**Table 12 Results of a 24-Week (LOCF\*) Placebo-Controlled Study of FORXIGA in Add-On Combination with Metformin**

<b>Efficacy Parameter</b>	<b>FORXIGA 5 mg + Metformin N=137<sup>†</sup></b>	<b>FORXIGA 10 mg + Metformin N=135<sup>†</sup></b>	<b>Placebo + Metformin N=137<sup>†</sup></b>
<b>HbA1c (%)</b>			
Baseline mean	8.17	7.92	8.11
Change from baseline (adjusted mean <sup>‡</sup> )	−0.70	−0.84	−0.30
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	−0.41 <sup>§</sup> (−0.61, −0.21)	−0.54 <sup>§</sup> (−0.74, −0.34)	
Patients (%) achieving HbA1c <7% adjusted for baseline	37.5 <sup>¶</sup>	40.6 <sup>¶</sup>	25.9
<b>FPG (mmol/L)</b>			
Baseline mean	9.4	8.7	9.2
Change from baseline at week 24 (adjusted mean <sup>‡</sup> )	−1.2	−1.3	−0.3
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	−0.9 <sup>§</sup> (−1.3, −0.5)	−1.0 <sup>§</sup> (−1.4, −0.6)	
<b>Body Weight (kg)</b>			
Baseline mean	84.73	86.28	87.74
Change from baseline (adjusted mean <sup>‡</sup> )	−3.04	−2.86	−0.89
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	−2.16 <sup>§</sup> (−2.81, −1.50)	−1.97 <sup>§</sup> (−2.63, −1.31)	

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

<sup>†</sup> All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.

<sup>‡</sup> Least squares mean adjusted for baseline value.

<sup>§</sup> p-value <0.0001 vs. placebo + metformin.

<sup>¶</sup> p-value <0.05 vs. placebo + metformin.

### ***Add-On Therapy with Metformin – Active-Controlled Study versus Glipizide (Study 3)***

Patients with T2DM with inadequate glycemic control (HbA1c >6.5% and ≤10%) were randomized in a 52-week, double-blind, glipizide-controlled non-inferiority study to evaluate FORXIGA 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 FORXIGA 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 FORXIGA had been titrated to the maximum study dose (10 mg), versus 73% treated with glipizide (20 mg). As shown in Table 13, treatment with FORXIGA 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 FORXIGA compared to glipizide.

**Table 13 Results at Week 52 (LOCF\*) in an Active-Controlled Study comparing FORXIGA to Glipizide as Add-on to Metformin**

Efficacy Parameter	FORXIGA + Metformin N=400 <sup>†</sup>	Glipizide + Metformin N=401 <sup>†</sup>
<b>HbA1c (%)</b>		
Baseline (mean)	7.69	7.74
Change from baseline (adjusted mean <sup>‡</sup> )	-0.52	-0.52
Difference from Glipizide+Metformin (adjusted mean <sup>‡</sup> ) (95% CI)	0.00 <sup>¶</sup> (-0.11, 0.11)	
<b>Body Weight (kg)</b>		
Baseline (mean)	88.44	87.60
Change from baseline (adjusted mean <sup>‡</sup> )	-3.22	1.44
Difference from Glipizide+Metformin (adjusted mean <sup>‡</sup> ) (95% CI)	-4.65 <sup>§</sup> (-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 a Sulfonylurea (Study 4)***

Patients with T2DM and inadequate glycemic control ( $\text{HbA1c} \geq 7\%$  and  $\leq 10\%$ ) were randomized in a 24-week, double-blind, placebo-controlled study to evaluate FORXIGA in combination with glimepiride (a sulfonylurea). Patients on at least half the maximum recommended dose of a glimepiride as monotherapy (4 mg) for at least 8 weeks lead-in were randomized to dapagliflozin 2.5 mg, FORXIGA 5 mg, or 10 mg or placebo in addition to glimepiride 4 mg per day. Down-titration of glimepiride to 2 mg or 0 mg was allowed for hypoglycemia during the treatment period; no up-titration of glimepiride was allowed.

As shown in Table 14, treatment with FORXIGA 5 mg and 10 mg in combination with glimepiride provided significant reductions in HbA1c, FPG, 2-hour PPG, and body weight relative to placebo plus glimepiride at Week 24 which were sustained long term.



**Table 14 Results of 24 Week (LOCF\*) Placebo-Controlled Study of FORXIGA in Combination with a Sulfonylurea (Glimepiride)**

<b>Efficacy Parameter</b>	<b>FORXIGA 5 mg + Glimepiride N=142<sup>†</sup></b>	<b>FORXIGA 10 mg + Glimepiride N=151<sup>†</sup></b>	<b>Placebo + Glimepiride N=145<sup>†</sup></b>
<b>HbA1c (%)</b>			
Baseline mean	8.12	8.07	8.15
Change from baseline (adjusted mean <sup>‡</sup> )	-0.63	-0.82	-0.13
Difference from placebo + glimepiride (adjusted mean <sup>‡</sup> ) (95% CI)	-0.49 <sup>§</sup> (-0.67, -0.32)	-0.68 <sup>§</sup> (-0.86, -0.51)	
Patients (%) achieving HbA1c <7% adjusted for baseline	30.3 <sup>§</sup>	31.7 <sup>§</sup>	13.0
<b>FPG (mmol/L)</b>			
Baseline mean	9.7	9.6	9.6
Change from baseline (adjusted mean <sup>‡</sup> )	-1.2	-1.6	-0.1
Difference from placebo + glimepiride (adjusted mean <sup>‡</sup> ) (95% CI)	-1.1 <sup>§</sup> (-1.5, -0.7)	-1.5 <sup>§</sup> (-1.9, -1.1)	
<b>2-hour PPG<sup>¶</sup> (mmol/L)</b>			
Baseline (mean)	17.9	18.3	18.0
Change from baseline (adjusted mean <sup>‡</sup> )	-3.0	-3.4	-0.6
Difference from placebo + glimepiride (adjusted mean <sup>‡</sup> ) (95% CI)	-2.4 <sup>§</sup> (-3.2, -1.5)	-2.7 <sup>§</sup> (-3.6, -1.9)	
<b>Body Weight (kg)</b>			
Baseline mean	81.00	80.56	80.94
Change from baseline (adjusted mean <sup>‡</sup> )	-1.56	-2.26	-0.72
Difference from placebo + glimepiride (adjusted mean <sup>‡</sup> ) (95% CI)	-0.84 <sup>§§</sup> (-1.47, -0.21)	-1.54 <sup>§</sup> (-2.17, -0.92)	

\* 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.

§§ p-value 0.0091 versus placebo.

¶ 2-hour PPG level as a response to a 75 g oral glucose tolerance test (OGTT).

#### ***Add-On Therapy with Metformin and a Sulfonylurea (Study 5)***

Patients with T2DM and inadequate glycemic control (HbA1c  $\geq 7\%$  and  $\leq 10.5\%$ ) participated in a 24-week, double-blind, placebo-controlled study to evaluate FORXIGA in combination with metformin and a sulfonylurea. Patients on a stable dose of metformin (immediate- or extended-release formulations)  $\geq 1500$  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 FORXIGA 10 mg or placebo. Dose-titration of FORXIGA 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 15, treatment with FORXIGA 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 FORXIGA 10 mg, and placebo, respectively ( $p < 0.05$ ).

**Table 15 Results of 24-Week (LOCF\*) Placebo-Controlled Study of FORXIGA in Combination with Metformin and Sulfonylurea**

<b>Efficacy Parameter</b>	<b>FORXIGA 10 mg + Metformin + Sulphonylurea N=108<sup>†</sup></b>	<b>Placebo + Metformin + Sulphonylurea N=108<sup>†</sup></b>
<b>HbA1c (%)</b>		
Baseline mean	8.08	8.24
Change from baseline (adjusted mean <sup>‡,‡‡</sup> )	-0.86	-0.17
Difference from placebo (adjusted mean <sup>‡,‡‡</sup> ) (95% CI)	-0.69 <sup>§</sup> (-0.89, -0.49)	
Patients (%) achieving HbA1c <7% adjusted for baseline	31.8 <sup>§</sup>	11.1
<b>FPG (mmol/L)</b>		
Baseline mean	9.3	10.0
Change from baseline at Week 24 (adjusted mean <sup>‡</sup> )	-1.9	-0.04
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-1.86 <sup>§</sup> (-2.4, -1.3)	
<b>Body Weight (kg)</b>		
Baseline mean	88.57	90.07
Change from baseline (adjusted mean <sup>‡</sup> )	-2.65	-0.58
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-2.07 <sup>§</sup> (-2.79, -1.35)	

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

<sup>†</sup> Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.

<sup>‡</sup> Least squares mean adjusted for baseline value based on ANCOVA model.

<sup>‡‡</sup> Least squares mean adjusted for baseline value based on a longitudinal repeated measures model

<sup>§</sup> p-value <0.0001 versus placebo.

### ***Add-On Combination Therapy with Sitagliptin Alone or in Combination with Metformin (Study 6)***

A total of 452 patients with T2DM 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 ( $\geq 1500$  mg/day) and within each stratum were randomized to either FORXIGA 10 mg plus sitagliptin 100 mg once daily or placebo plus sitagliptin 100 mg once daily. Endpoints were tested for FORXIGA 10 mg versus placebo for the total study group (sitagliptin with and without metformin) and for each stratum (sitagliptin alone or sitagliptin with metformin).

As shown in Table 16, statistically significant ( $p < 0.0001$ ) reductions in HbA1c, FPG and body weight relative to placebo were observed with FORXIGA 10 mg treatment for the total study group (sitagliptin with and without metformin) and for each stratum (sitagliptin alone or sitagliptin with metformin) at Week 24.

**Table 16 Results of a 24-Week (LOCF\*) Placebo-Controlled Study of FORXIGA in Add-On Combination with Sitagliptin with or without Metformin (Full Analysis Set and Strata without or with Metformin)**

<b>Efficacy Parameter</b>	<b>FORXIGA 10 mg + Sitagliptin + or –Met N=223<sup>†</sup></b>	<b>Placebo + Sitagliptin + or –Met N=224<sup>†</sup></b>	<b>FORXIGA 10 mg + Sitagliptin N=110<sup>†</sup></b>	<b>Placebo + Sitagliptin N=111<sup>†</sup></b>	<b>FORXIGA 10 mg + Sitagliptin +Met N=113<sup>†</sup></b>	<b>Placebo + Sitagliptin +Met N=113<sup>†</sup></b>
<b>HbA1c (%)</b>	N=223	N=223	N=110	N=110	N=113	N=113
Baseline (mean)	7.90	7.97	7.99	8.07	7.80	7.87
Change from baseline (adjusted mean <sup>‡</sup> )	–0.45	0.04	–0.47	0.10	–0.43	–0.02
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	–0.48 <sup>§</sup> (–0.62, –0.34)		–0.56 <sup>§</sup> (–0.79, –0.34)		–0.40 <sup>§</sup> (–0.58, –0.23)	
<b>FPG (mmol/L)</b>	N=222	N=222	N=110	N=110	N=112	N=112
Baseline (mean)	8.97	9.05	8.73	8.96	9.21	9.14
Change from baseline at Week 24 (adjusted mean <sup>‡</sup> )	–1.34	0.21	–1.22	0.26	–1.45	0.17
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	–1.55 <sup>§</sup> (–1.91, –1.19)		–1.47 <sup>§</sup> (–2.01, –0.94)		–1.62 <sup>§</sup> (–2.11, –1.13)	
<b>Body Weight (kg)</b>	N=223	N=224	N=110	N=111	N=113	N=113
Baseline (mean)	91.02	89.23	88.01	84.20	93.95	94.17
Change from baseline (adjusted mean <sup>‡</sup> )	–2.14	–0.26	–1.91	–0.06	–2.35	–0.47

**Table 16 Results of a 24-Week (LOCF\*) Placebo-Controlled Study of FORXIGA in Add-On Combination with Sitagliptin with or without Metformin (Full Analysis Set and Strata without or with Metformin)**

Efficacy Parameter	FORXIGA 10 mg + Sitagliptin + or –Met N=223 <sup>†</sup>	Placebo + Sitagliptin + or –Met N=224 <sup>†</sup>	FORXIGA 10 mg + Sitagliptin N=110 <sup>†</sup>	Placebo + Sitagliptin N=111 <sup>†</sup>	FORXIGA 10 mg + Sitagliptin +Met N=113 <sup>†</sup>	Placebo + Sitagliptin +Met N=113 <sup>†</sup>
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	–1.89 <sup>§</sup> (–2.37, –1.40)		–1.85 <sup>§</sup> (–2.47, –1.23)		–1.87 <sup>§</sup> (–2.61, –1.13)	

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

<sup>†</sup> Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.

<sup>‡</sup> Least squares mean adjusted for baseline value.

<sup>§</sup> p-value <0.0001 versus placebo.

#### ***Add-On Therapy with Insulin (Study 7)***

Patients with T2DM 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 FORXIGA 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, FORXIGA 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  $\geq 1500$  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, FORXIGA 5 mg and 10 mg doses provided significant improvement in HbA1c and mean insulin dose, and a significant reduction in body weight compared with placebo (Table 17); the effect of FORXIGA on HbA1c was similar in patients in both strata.

**Table 17 Results of 24 Week (LOCF\*) Placebo-Controlled Study of FORXIGA in Combination with Insulin with or without up to 2 Oral Antidiabetic Therapies<sup>§§</sup>**

<b>Efficacy Parameter</b>	<b>FORXIGA 5 mg + Insulin N=211<sup>†</sup></b>	<b>FORXIGA 10 mg + Insulin N=194<sup>†</sup></b>	<b>Placebo + Insulin N=193<sup>†</sup></b>
<b>HbA1c (%)</b>			
Baseline mean	8.61	8.58	8.46
Change from baseline (adjusted mean <sup>‡</sup> )	-0.82	-0.90	-0.30
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-0.52 <sup>§</sup> (-0.66, -0.38)	-0.60 <sup>§</sup> (-0.74, -0.45)	
<b>FPG (mmol/L)</b>			
Baseline mean	10.3	9.6	9.4
Change from baseline (adjusted mean <sup>‡</sup> )	-1.0	-1.2	0.2
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-1.2 (-1.7, -0.7)	-1.4 <sup>§</sup> (-1.9, -0.9)	
<b>Body Weight (kg)</b>			
Baseline mean	93.20	94.63	94.21
Change from baseline (adjusted mean <sup>‡</sup> )	-0.98	-1.67	0.02
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-1.00 <sup>§</sup> (-1.50, -0.50)	-1.68 <sup>§</sup> (-2.19, -1.18)	

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

<sup>†</sup> Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.

<sup>‡</sup> Least squares mean adjusted for baseline value.

<sup>§</sup> p-value <0.0001 versus placebo.

<sup>§§</sup> Use with oral antidiabetic combinations other than metformin alone is not indicated.

### ***Cardiovascular Outcomes in Patients with T2DM (Study 8)***

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

then tested superiority of the dual primary efficacy endpoints of MACE and the composite of hospitalization for heart failure or cardiovascular death, in parallel<sup>2</sup>.

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

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

The mean age of the study population was 63.9 years, 37.4% were female, 79.6% were White, 3.5% Black or African-American, and 13.4% Asian. Approximately 46% of patients treated with FORXIGA were 65 years and older and 6.3% were 75 years and older. In total, 22.4% had had diabetes for  $\leq 5$  years, and the mean duration of diabetes was 11.9 years. Mean HbA1c was 8.3% and mean BMI was 32.0 kg/m<sup>2</sup>. At baseline, 10.0% of patients had a history of HF. Mean eGFR was 85.2 mL/min/1.73m<sup>2</sup>, 7.4% of patients had eGFR  $< 60$  mL/min/1.73m<sup>2</sup> and 45.1% had eGFR  $\geq 60$  to  $< 90$  mL/min/1.73m<sup>2</sup>. At baseline, 30.3% of patients had micro- or macroalbuminuria (urine albumin to creatinine ratio  $\geq 30$  to  $\leq 300$  mg/g or  $> 300$  mg/g, respectively). Most patients (98.1%) used one or more diabetic medications at baseline: 82.0% of the patients were being treated with metformin, 40.9% with insulin, 42.7% with a sulfonylurea, 16.8% with a DPP-4 inhibitor, and 4.4% with a GLP-1 receptor agonist. Approximately 81.3% of patients were treated with ACE inhibitors or ARB, 75.0% with statins, 61.1% with antiplatelet therapy, 55.5% with acetylsalicylic acid, 52.6% with beta-blockers, 34.9% with calcium channel blockers, 22.0% with thiazide diuretics, and 10.5% with loop diuretics.

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

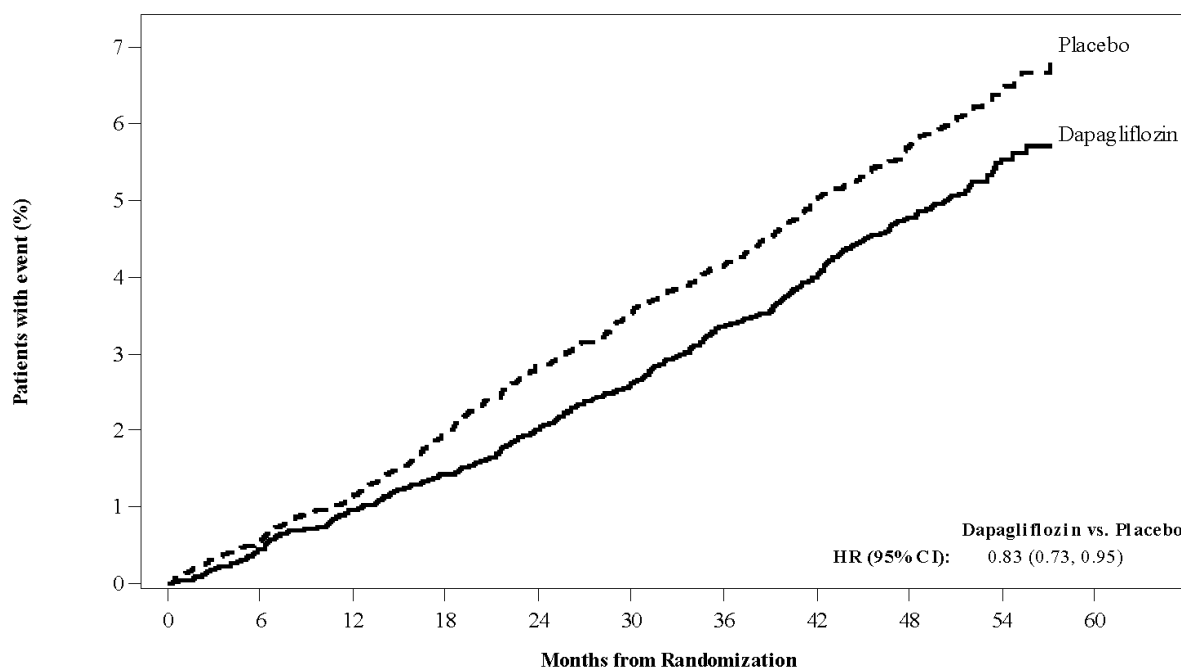
FORXIGA was superior to placebo in reducing the incidence of the primary composite endpoint of hospitalization for HF or CV death, representing a 17% reduction in risk (HR 0.83 [95% CI 0.73, 0.95];  $p = 0.005$ ) (Figure 1). Analyses of the single components suggest that the

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<sup>2</sup> Dual primary efficacy endpoints may be used when success on either endpoint could independently support a conclusion of effectiveness. The dual primary efficacy endpoints in DECLARE-TIMI 58 were tested independently and in parallel. Type I error was controlled by splitting the  $\alpha$  between the dual primary endpoints.

difference in treatment effect was driven by hospitalization for HF (HR 0.73 [95% CI 0.61, 0.88]), with no clear difference in CV death (HR 0.98 [95% CI 0.82 to 1.17]) (Figure 2).

**Figure 1 Time to First Occurrence of Hospitalization for Heart Failure or Cardiovascular Death in the DECLARE-TIMI 58 Study**

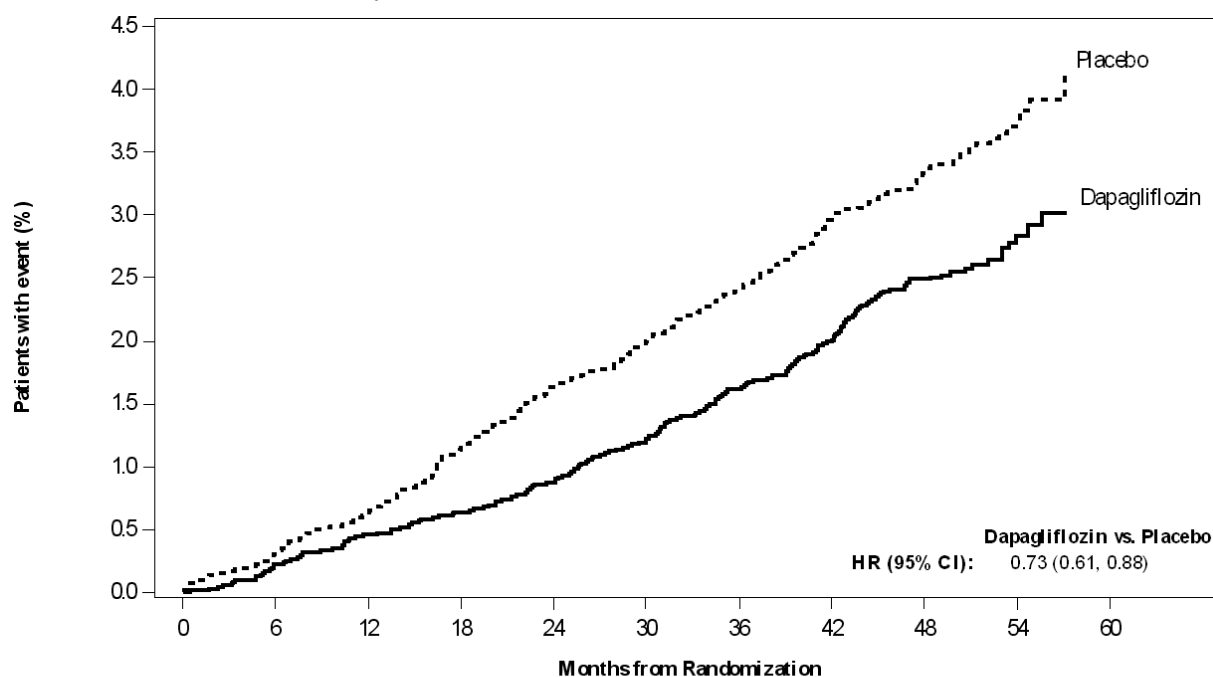


**Patients at risk**

Dapagliflozin:	8582	8517	8415	8322	8224	8110	7970	7497	5445	1626
Placebo:	8578	8485	8387	8259	8127	8003	7880	7367	5362	1573

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

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



**Patients at risk**

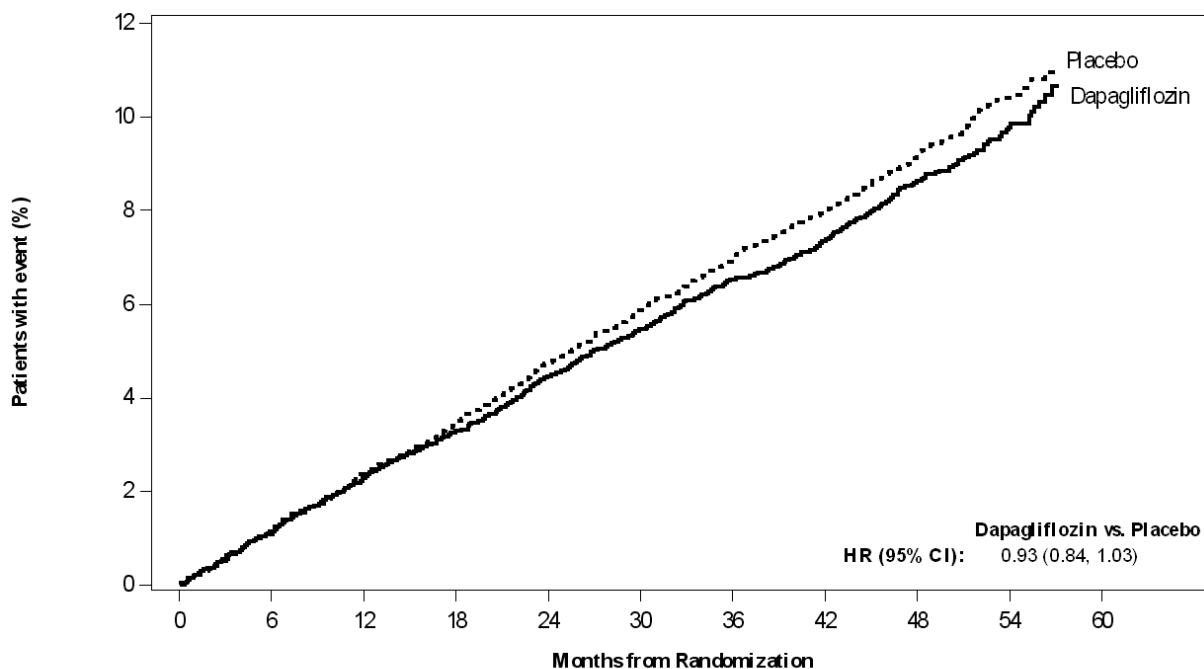
Dapagliflozin:	8582	8509	8403	8315	8218	8101	7965	7489	5439	1626
Placebo:	8578	8482	8380	8256	8121	7998	7874	7360	5358	1572

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

Superiority of FORXIGA over placebo was not demonstrated for MACE (HR 0.93 [95% CI 0.84, 1.03];  $p=0.172$ ) (Figure 3, Table 18). Analyses of the single components of MACE show that the incidence of MI was numerically lower in the dapagliflozin group compared with the placebo group (HR 0.89 [95% CI 0.77 to 1.01]), with no clear difference observed for CV death or ischemic stroke.



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



**Patients at risk**

Dapagliflozin:	8582	8466	8303	8166	8017	7873	7708	7237	5225	1548
Placebo:	8578	8433	8281	8129	7969	7805	7649	7137	5158	1501

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

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

**Table 18 Treatment Effects for the Composite Endpoints\* and Their Components in the DECLARE Study**

Efficacy Parameter	Patients with events, n (%)		Hazard ratio (95% CI) <sup>†</sup>	p- value <sup>‡</sup>
	FORXIGA 10 mg N=8582	Placebo N=8578		
<b>Composite of Hospitalization for HF, CV Death</b>	417 (4.9)	496 (5.8)	0.83 (0.73, 0.95)	0.005
Hospitalization for HF §	212 (2.5)	286 (3.3)	0.73 (0.61, 0.88)	<0.001
CV Death§	245 (2.9)	249 (2.9)	0.98 (0.82, 1.17)	0.830
<b>Composite Endpoint of CV Death, MI, Ischemic Stroke</b>	756 (8.8)	803 (9.4)	0.93 (0.84, 1.03)	0.172
CV Death§	245 (2.9)	249 (2.9)	0.98 (0.82, 1.17)	0.830
Myocardial Infarction§	393 (4.6)	441 (5.1)	0.89 (0.77, 1.01)	0.080
Ischemic Stroke§	235 (2.7)	231 (2.7)	1.01 (0.84, 1.21)	0.916
<b>Renal Composite Endpoint§§</b>	370 (4.3)	480 (5.6)	0.76 (0.67, 0.87)	
<b>All-Cause Mortality</b>	529 (6.2)	570 (6.6)	0.93 (0.82, 1.04)	

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

\* Full analysis set

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

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

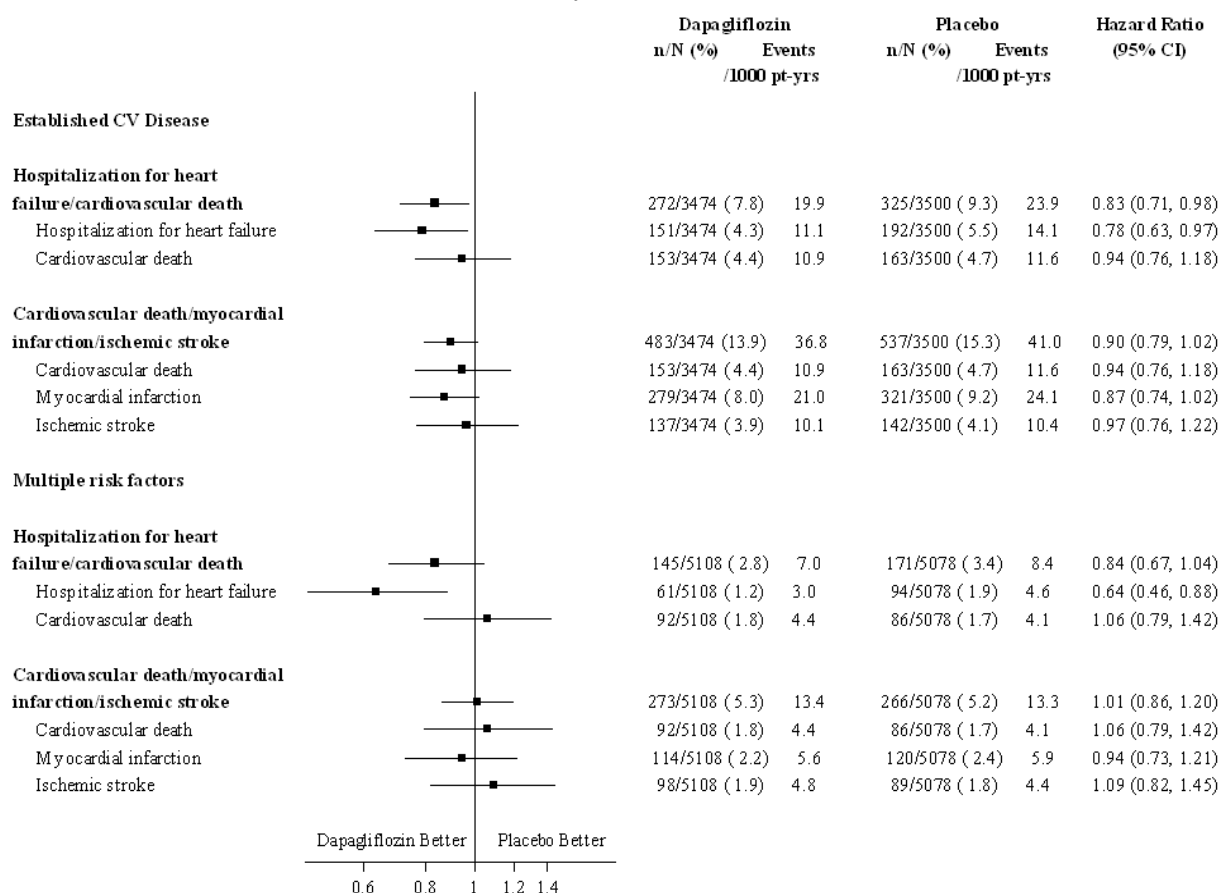
§ The components of the composite endpoints were exploratory variables.

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

Patients in DECLARE-TIMI 58 were stratified by CV risk category (CV risk factors or established CV disease). The benefit of FORXIGA over placebo in reducing the risk of

hospitalization for heart failure was observed both in patients with and without established CV disease (Figure 4) and was consistent across key subgroups including age (>65 and ≥65 years, and <75 and ≥75 years), gender, renal function (eGFR), and region. There was a trend towards an effect of dapagliflozin on MACE in patients with established CV disease at baseline and neutral results in patients with CV risk factors (Figure 4).

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



Time to first event was analysed in a Cox proportional hazards model.  
CI=Confidence interval

## Other Studies in Patients with T2DM Treated for Glycemic Control

### *Use in Patients with Type 2 Diabetes and Renal Impairment*

*Mild renal impairment (eGFR ≥60 to <90 mL/min/1.73m<sup>2</sup>):*

Efficacy was assessed in a pooled analysis across 9 clinical studies consisting of 2226 patients with mild renal impairment. The mean change from baseline in HbA1c and the placebo-corrected mean HbA1c reduction at 24 weeks was -1.03% and -0.54%, respectively for FORXIGA 5 mg (n=545) and -1.03% and -0.54%, respectively for FORXIGA 10 mg (n=562).

The safety profile in patients with mild renal impairment is similar to that in the overall population.

The efficacy of FORXIGA was assessed in two dedicated studies of patients with moderate renal impairment and in a pooled analysis.

*Moderate renal impairment CKD 3A (eGFR  $\geq 45$  to  $< 60$  mL/min/1.73m<sup>2</sup>):*

The efficacy of dapagliflozin was assessed in a dedicated study in diabetic patients with an eGFR  $\geq 45$  to  $< 60$  mL/min/1.73m<sup>2</sup> who had inadequate glycemic control. In a randomized, double blind, placebo-controlled trial a total of 321 adult patients with T2DM and eGFR  $\geq 45$  to  $< 60$  mL/min/1.73m<sup>2</sup> (moderate renal impairment subgroup CKD 3A), with inadequate glycemic control, were treated with FORXIGA 10 mg or placebo. At Week 24, FORXIGA 10 mg (n=159) resulted in statistically significant reductions in HbA1c and body weight compared with placebo (n=161) (Table 19).

**Table 19**                      **Results at Week 24 in a Placebo-Controlled Study of FORXIGA Treatment in Diabetic Patients with Moderate Renal Impairment (CKD 3A, eGFR  $\geq 45$  to  $< 60$  mL/min/1.73m<sup>2</sup>)**

<b>Efficacy Parameter</b>	<b>FORXIGA 10 mg N=159</b>	<b>Placebo N=161</b>
<b>HbA1c (%)</b>		
Baseline (mean)	8.35	8.03
Change from baseline (adjusted mean <sup>*</sup> )	-0.37 <sup>§</sup>	-0.03
Difference from placebo (adjusted mean <sup>*</sup> ) (95% CI)	-0.34 <sup>§</sup> (-0.53, -0.15)	
<b>Body Weight (kg)</b>		
Baseline (mean)	92.51	88.30
% Change from baseline (adjusted mean <sup>*</sup> )	-3.42 <sup>§</sup>	-2.02
Difference from placebo (adjusted mean <sup>*</sup> ) (95% CI)	-1.43 <sup>§</sup> (-2.15, -0.69)	

\* Least squares mean adjusted for baseline value.

§ p-value  $< 0.001$ .

*Moderate renal impairment (eGFR  $\geq 30$  to  $< 60$  mL/min/1.73m<sup>2</sup>):*

The efficacy of FORXIGA was assessed in a study of 252 diabetic patients with eGFR  $\geq 30$  to  $< 60$  mL/min/1.73m<sup>2</sup>. FORXIGA treatment did not show a significant placebo corrected change in HbA1c in the overall study population at 24 weeks. In an additional analysis of the subgroup CKD 3A (eGFR  $\geq 45$  to  $< 60$  mL/min/1.73m<sup>2</sup>), FORXIGA 5 mg (n=35) provided a placebo-corrected mean HbA1c change at 24 weeks of -0.37% (95% CI: -0.83, 0.10), and

FORXIGA 10 mg (n=32) provided a placebo-corrected mean HbA1c change at 24 weeks of -0.33% (95% CI: -0.80, 0.14).

Efficacy in patients with moderate renal impairment was assessed in a pooled analysis across 9 clinical studies (366 patients, 87% with eGFR  $\geq 45$  to  $< 60$  mL/min/1.73m<sup>2</sup>); this pool did not include the two dedicated studies of diabetic patients with moderate renal impairment. The mean change from baseline in HbA1c and the placebo-corrected mean HbA1c reduction at 24 weeks was -0.71% (95% CI: -0.89, -0.53) and -0.23% (95% CI: -0.47, 0.02), respectively, for FORXIGA 5 mg (n=102) and -0.87% (95% CI: -1.07, -0.68) and -0.39% (95% CI: -0.65, -0.14), respectively, for FORXIGA 10 mg (n=85).

#### ***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 T2DM and CVD were randomized and treated with FORXIGA 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 FORXIGA 10 mg had hypertension at entry, and the most common qualifying CV events were coronary heart disease (76%) or stroke (20%). Approximately 19% of patients received loop diuretics during the studies and 14% had congestive heart failure (1% had NYHA Class III). Approximately 37% of patients received metformin plus one additional OAD (sulfonylurea, thiazolidinedione, DPP4-inhibitor, or other OAD with or without insulin at entry), 38% received insulin plus at least one OAD, and 18% received insulin alone.

For both studies, at Week 24 treatment with FORXIGA 10 mg provided significant improvement in HbA1c compared with placebo (Table 20). Significant reductions in total body weight and seated systolic blood pressure were also seen in patients treated with FORXIGA 10 mg compared with placebo. For both studies, reductions in HbA1c and body weight were generally maintained at Week 52 and Week 104.

**Table 20 Results at Week 24 (LOCF\*) in Two Placebo-Controlled Studies Comparing FORXIGA to Placebo in Patients with Type 2 Diabetes and Cardiovascular Disease**

Efficacy Parameter	Study 8 (D1690C00018)		Study 9 (D1690C00019)	
	FORXIGA 10 mg + Usual Treatment N=455 <sup>†</sup>	Placebo + Usual Treatment N=459 <sup>†</sup>	FORXIGA 10 mg + Usual Treatment N=480 <sup>†</sup>	Placebo + Usual Treatment N=482 <sup>†</sup>
<b>HbA1c (%)</b>				
Baseline mean	8.18	8.08	8.04	8.07
Change from baseline (adjusted mean <sup>‡</sup> )	-0.38	0.08	-0.33	0.07

**Table 20 Results at Week 24 (LOCF\*) in Two Placebo-Controlled Studies Comparing FORXIGA to Placebo in Patients with Type 2 Diabetes and Cardiovascular Disease**

	<b>Study 8 (D1690C00018)</b>		<b>Study 9 (D1690C00019)</b>	
<b>Efficacy Parameter</b>	<b>FORXIGA 10 mg + Usual Treatment N=455<sup>†</sup></b>	<b>Placebo + Usual Treatment N=459<sup>†</sup></b>	<b>FORXIGA 10 mg + Usual Treatment N=480<sup>†</sup></b>	<b>Placebo + Usual Treatment N=482<sup>†</sup></b>
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-0.46 <sup>§</sup> (-0.56, -0.37)		-0.40 <sup>§</sup> (-0.50, -0.30)	
<b>Body Weight (kg)</b>				
Baseline mean	92.63	93.59	94.53	93.22
Change from baseline (adjusted percent <sup>‡</sup> )	-2.56	-0.30	-2.53	-0.61
Difference from placebo (adjusted percent <sup>‡</sup> ) (95% CI)	-2.27 <sup>§</sup> (-2.64, -1.89)		-1.93 <sup>§</sup> (-2.31, -1.54)	

\* LOCF: last observation carried forward.

<sup>†</sup> Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.

<sup>‡</sup> Least squares mean adjusted for baseline value.

<sup>§</sup> p-value <0.0001.

### ***Blood Pressure***

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

### ***Bone Mineral Density and Body Composition in Type 2 Diabetic Patients<sup>2</sup>***

A 24-week study (n=182) found a greater reduction in total body weight from baseline to Week 24 in patients taking FORXIGA 10 mg plus metformin (-2.96 kg), versus placebo plus metformin (-0.88 kg), with a significant interaction for gender [greater weight loss for males (-2.76 kg) than females (-1.22 kg)]. The reduction in total body fat mass from baseline to Week 24 was -2.22 kg for FORXIGA and -0.74 kg for placebo with a reduction in percentage total body fat mass from baseline to Week 24 in the dapagliflozin group of 1%, whereas there was little change in the placebo group, as evaluated by dual energy x-ray absorptiometry (DXA).

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%).

### **Clinical Trial in Patients with Heart Failure (Study 9)**

Dapagliflozin And Prevention of Adverse outcomes in Heart Failure (DAPA-HF) was an international, multicenter, randomized, double-blind, placebo-controlled study in patients with heart failure (New York Heart Association [NYHA] functional class II-IV) with reduced ejection fraction (left ventricular ejection fraction [LVEF]  $\leq 40\%$ ) to determine the effect of FORXIGA compared with placebo, when added to background standard of care therapy, on the incidence of CV death, hospitalization for heart failure or urgent heart failure visit.

Of 4744 patients, 2373 were randomized to FORXIGA 10 mg and 2371 to placebo and followed for a median of 18 months. The mean age of the study population was 66 years (36% of patients were between the ages of 66-75 years and 21% of patients were over 75 years), 77% were male, 70% White, 5% Black or African-American and 24% Asian.

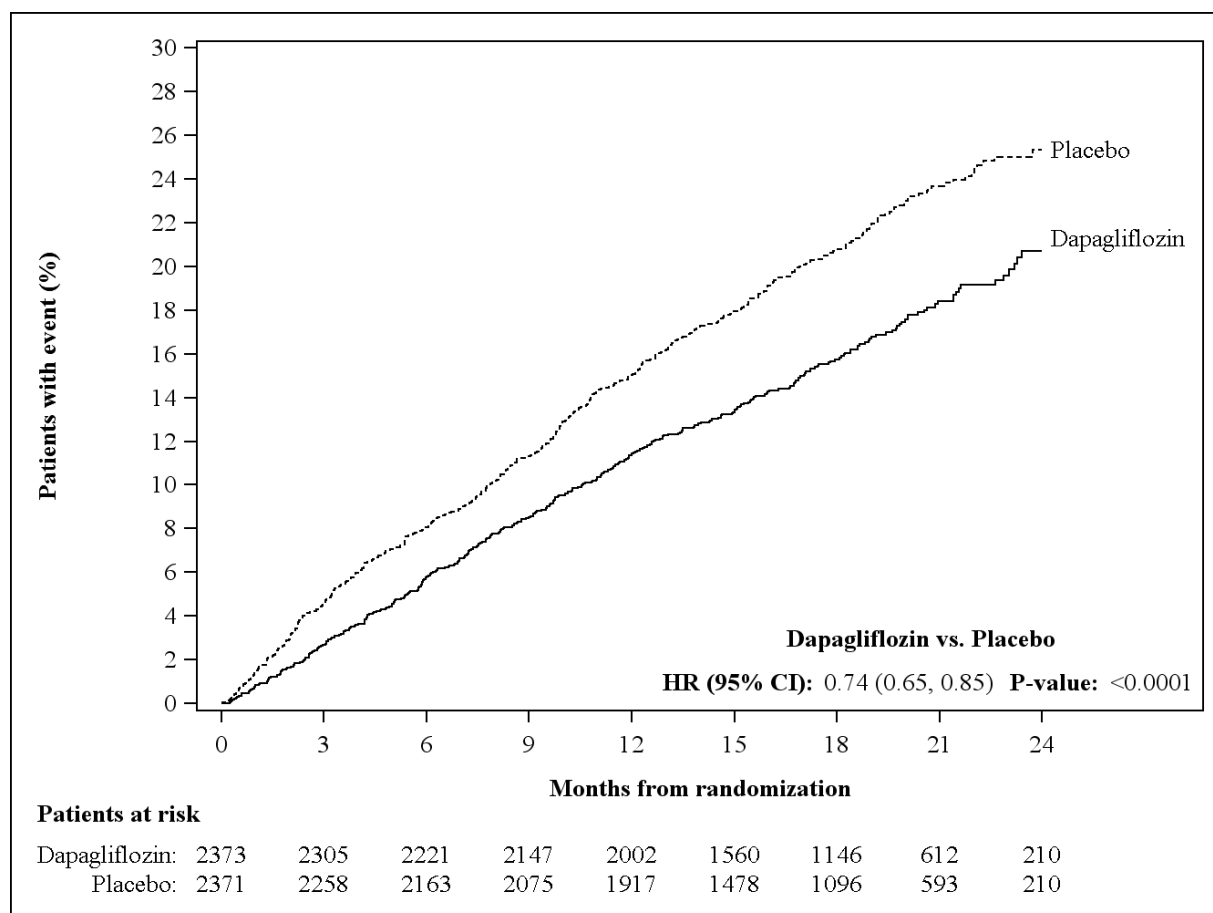
At baseline, 67.5% patients were classified as NYHA class II, 31.6% class III and 0.9% class IV, median LVEF was 32%, 42% of the patients in each treatment group had a history of T2DM, and an additional 3% of the patients in each group were classified as having T2DM based on an HbA1c  $\geq 6.5\%$  at both enrollment and randomization.

At baseline all patients were on standard of care therapy. Ninety four percent of patients were treated with ACEi, ARB, or angiotensin receptor-neprilysin inhibitor (ARNI, 11%), 96% with beta-blocker, 71% with mineralocorticoid receptor antagonist (MRA), 93% with diuretic and 26% had an implantable device.

Patients with eGFR  $\geq 30$  mL/min/1.73m<sup>2</sup> at enrollment were included in the study. The mean eGFR was 66 mL/min/1.73m<sup>2</sup>, 41% of patients had eGFR <60mL/min/1.73m<sup>2</sup> and 15% had eGFR <45 mL/min/1.73m<sup>2</sup>.

FORXIGA demonstrated a statistically significant reduction in the incidence of the primary composite endpoint of CV death, hospitalization for heart failure or urgent heart failure visit vs placebo (HR 0.74 [95% CI 0.65, 0.85];  $p < 0.0001$ ). The FORXIGA and placebo event curves separated early and continued to diverge over the study period (Figure 5).

**Figure 5** Time to first occurrence of the composite hospitalization of cardiovascular death, hospitalization for heart failure or urgent heart failure visit



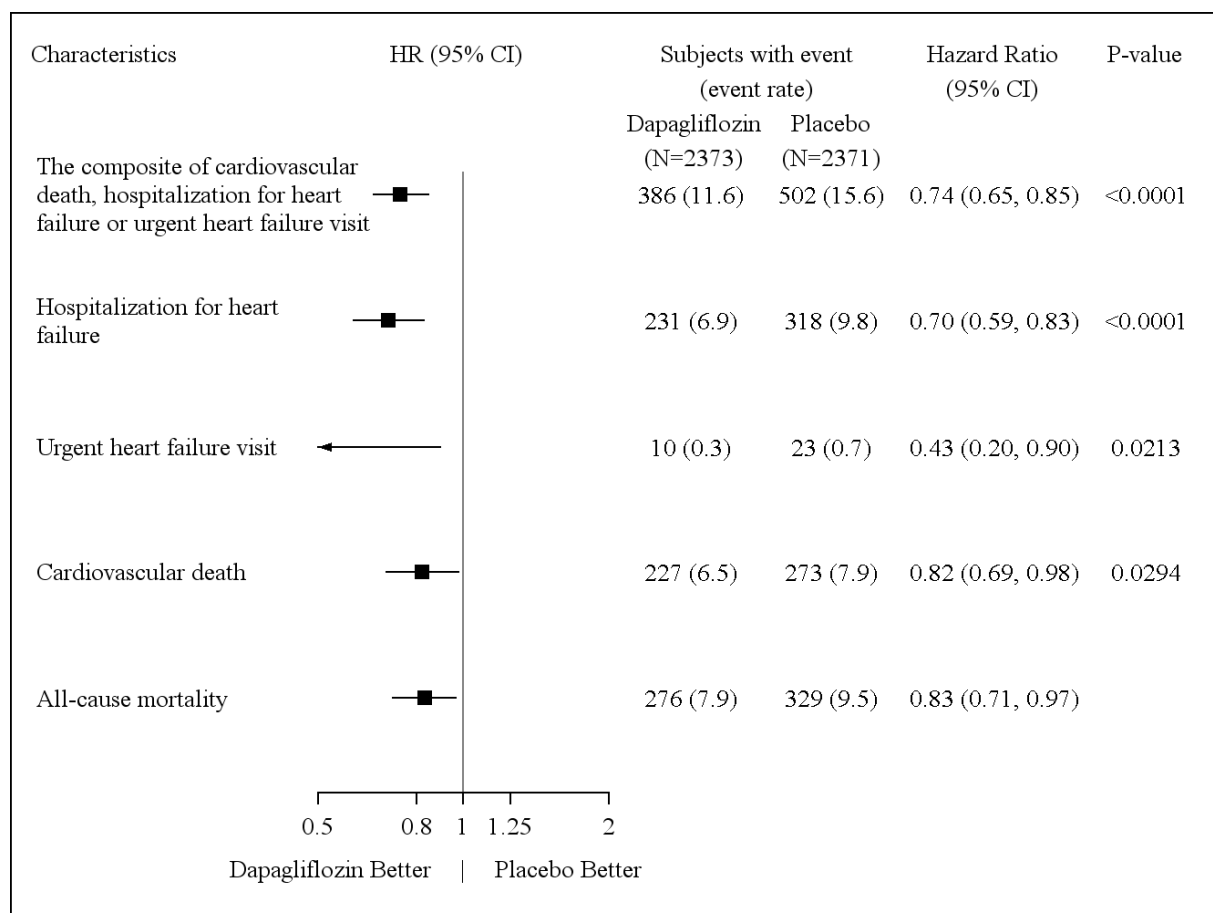
An urgent heart failure visit was defined as an urgent, unplanned, assessment by a physician, e.g. in an Emergency department, and requiring treatment for worsening heart failure (other than just an increase in oral diuretics).

Patients at risk is the number of patients at risk at the beginning of the period.

All three components of the primary composite endpoint individually contributed to the treatment effect (Figure 6). There were few urgent heart failure visits. FORXIGA also reduced the incidence of CV death or hospitalization for heart failure (HR 0.75 [95% CI 0.65, 0.85],  $p < 0.0001$ ).



**Figure 6 Treatment effects for the primary composite endpoint and its components**



An urgent heart failure visit was defined as an urgent, unplanned, assessment by a physician, e.g. in an Emergency Department, and requiring treatment for worsening heart failure (other than just an increase in oral diuretics).

The number of first events for the single components are the actual number of first events for each component and does not add up to the number of events in the composite endpoint.

Event rates are presented as the number of subjects with event per 100 patient years of follow-up.

p-values for single components are nominal.

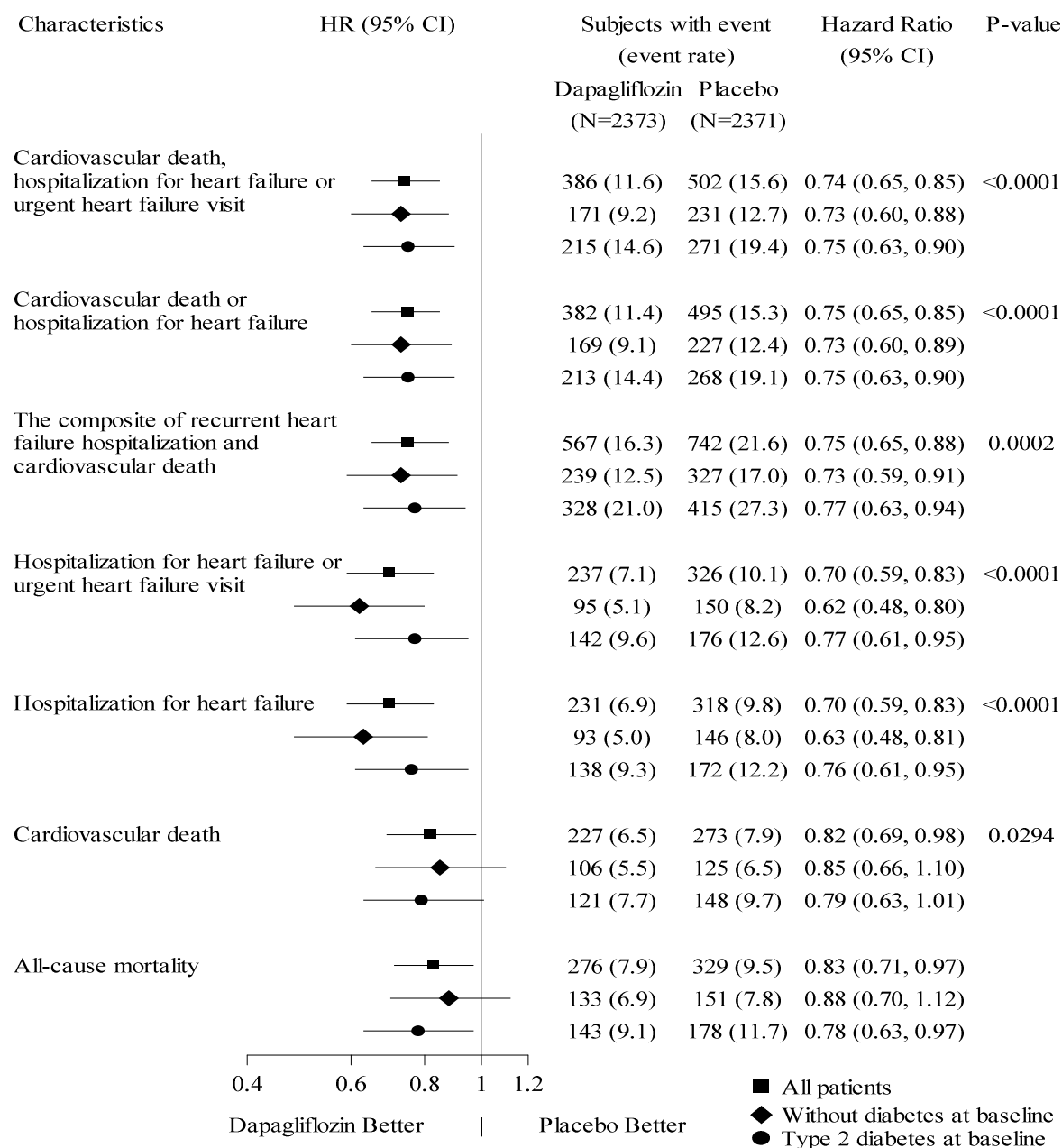
Superiority of dapagliflozin versus placebo for secondary endpoints was tested in a hierarchical testing sequence.

As the renal composite endpoint, preceding all-cause mortality in the sequence, was not statistically significant, all-cause mortality was not tested as part of the confirmatory testing.

FORXIGA also reduced the total number of events of hospitalizations for heart failure (first and recurrent) and CV death; there were 567 events in the FORXIGA group versus 742 events in the placebo group (Rate Ratio 0.75 [95% CI 0.65, 0.88]; p=0.0002).

The treatment benefit of FORXIGA was observed in heart failure patients both with T2DM and without diabetes (Figure 7).

**Figure 7 Treatment effects in all patients, in patients with T2DM and in patients without diabetes**



An urgent heart failure visit was defined as an urgent, unplanned, assessment by a physician, e.g. in an Emergency Department, and requiring treatment for worsening heart failure (other than just an increase in oral diuretics).

For the composite of recurrent hospitalizations for heart failure and cardiovascular death, rate ratios are presented rather than hazard ratios and the numbers of events are shown rather than subjects with event.

The number of first events for the single components are the actual number of first events for each component and does not add up to the number of events in the composite endpoint.

Event rates are presented as the number of subjects with event per 100 patient years of follow-up, or, for the composite of recurrent heart failure hospitalizations and CV death, as the average number of events per 100 patient years.

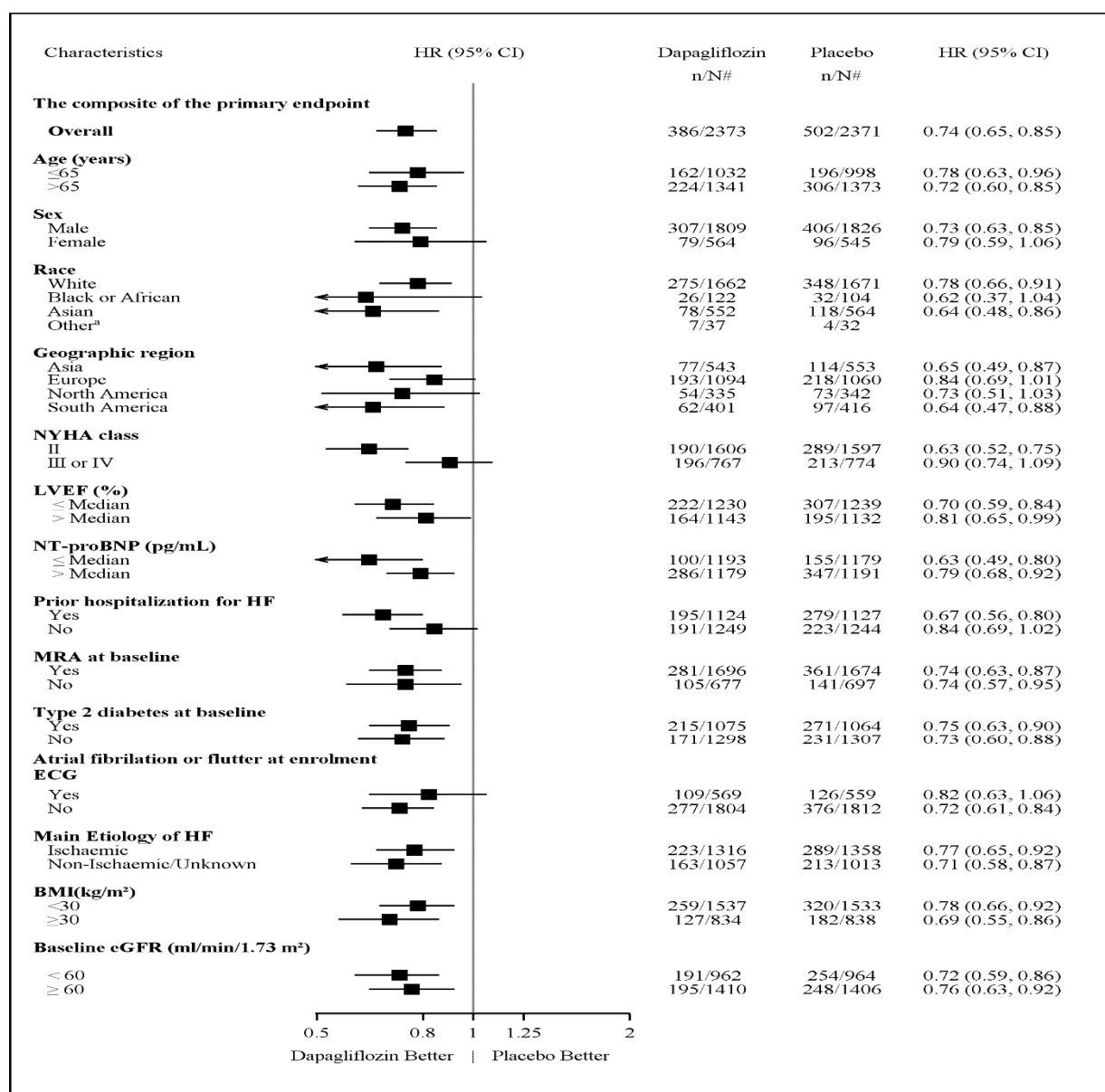
p-values for components of the primary composite endpoint are nominal.

Superiority of dapagliflozin versus placebo for secondary endpoints was tested in a hierarchical testing sequence.

As the renal composite endpoint, preceding all-cause mortality in the sequence, was not statistically significant, all-cause mortality was not tested as part of the confirmatory testing.

The treatment benefit of FORXIGA over placebo on the primary endpoint was also consistent across other key subgroups (Figure 8).

**Figure 8 Treatment effects for the primary composite endpoint by sub-groups**



<sup>a</sup> Hazard ratio estimates are not presented for subgroups with less than 15 events in total, both arms combined.  
n/N# Number of subjects with event/number of subjects in the subgroup.  
NT-proBNP = N-terminal pro b-type natriuretic peptide. HF = Heart failure

### *Patient Report Outcomes – heart failure symptoms*

The treatment effect of FORXIGA on heart failure symptoms was assessed by the Total Symptom Score of the Kansas City Cardiomyopathy Questionnaire (KCCQ-TSS), which quantifies heart failure symptom frequency and severity, including fatigue, peripheral edema, dyspnea and orthopnea. The score ranges from 0 to 100, with higher scores representing better health status.

Treatment with FORXIGA resulted in a statistically significant and clinically meaningful benefit over placebo in heart failure symptoms, as measured by change from baseline to Month 8 in the KCCQ-TSS, (Win Ratio 1.18 [95% CI 1.11, 1.26];  $p < 0.0001$ ). Both symptom frequency and symptom burden contributed to the results. Benefit was seen both in improving heart failure symptoms and in preventing deterioration of heart failure symptoms.

In responder analyses, the proportion of patients with a clinically meaningful improvement on the KCCQ-TSS from baseline at 8 months, defined as 5 points or more, was higher for the dapagliflozin treatment group compared with placebo (adjusted odds ratio [OR] 1.15, 95% CI 1.08-1.23). The proportion of patients with a clinically meaningful deterioration, defined as 5 points or more, was lower for the dapagliflozin treatment group compared to placebo (OR 0.84, 95% CI 0.78-0.90). The benefits observed with dapagliflozin remained when applying more conservative cut-offs for larger clinically meaningful change, 10-point increase (OR 1.15, 95% CI 1.08-1.22), 15-point increase (OR 1.14, 95% CI 1.07-1.22) and 10-point decrease (OR 0.85, 95% CI 0.79-0.92).

## **DETAILED PHARMACOLOGY**

The sodium-glucose cotransporter 2 (SGLT2) is selectively expressed in the kidney<sup>3</sup> 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  $K_i$  (inhibition constant) value for human SGLT2 is 0.2 nM with selectivity vs. human SGLT1 of 1200:1. 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.

## TOXICOLOGY

### Acute and repeat-dose toxicity

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  $\leq 25$  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  $0.465\text{ }\mu\text{g}\cdot\text{h/mL}$ , and in dogs for up to 12 months at doses of  $\leq 120$  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 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  $72\times$  (males) and  $105\times$  (females) the human AUC at the MRHD. In rats, AUC exposures were approximately  $131\times$  (males) and  $186\times$  (females) the human AUC at the MRHD. In a 6-month bladder tumour initiation-promotion study in rats with dapagliflozin (7 times MRHD), the results showed that dapagliflozin does not act as promoter or progressor of bladder cancer.

### **Mutagenesis**

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  $\geq 100\text{ }\mu\text{g/mL}$ . 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.

## Reproduction

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.

## Development

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× and 137×, respectively, the human values at the MHRD). Dose-related reductions in pup body weights were observed at doses  $\geq 15$  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× the human value at the MRHD).

In embryo-fetal development studies in rats and rabbits, dapagliflozin was administered for intervals coinciding with the major periods of organogenesis in each species. Neither maternal nor developmental toxicities were observed in rabbits up to the highest dose of 180 mg/kg/day (184× the MRHD). In rats, dapagliflozin was not teratogenic at doses up to 75 mg/kg/day (1441× the MRHD). Doses  $\geq 150$  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.

## PART III: CONSUMER INFORMATION

**Pr FORXIGA®**

dapagliflozin tablets

(as dapagliflozin propanediol monohydrate)

Read this carefully before you start taking FORXIGA 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 FORXIGA.

### ABOUT THIS MEDICATION

#### WHAT THE MEDICATION IS USED FOR:

##### **Type 2 diabetes**

FORXIGA is used along with diet and exercise to improve blood sugar levels in adults with type 2 diabetes. FORXIGA can be used:

- alone, if you cannot take metformin,
- with metformin,
- with a sulfonylurea,
- with metformin and a sulfonylurea,
- with sitagliptin (with or without metformin),
- with insulin (with or without metformin).

FORXIGA can also be used along with diet and exercise if you have type 2 diabetes and:

- an increased cardiovascular risk. This means that you have or are at risk of developing health problems due to your heart and blood vessels. FORXIGA can be used to reduce your risk of hospitalization due to heart failure.

##### **Heart Failure**

FORXIGA can be used in adults along with other heart failure medicines when your heart is unable to pump blood as well as normal to:

- reduce your risk of cardiovascular death,
- reduce your risk of hospitalization or urgent visits for heart failure.

#### WHAT IT DOES:

FORXIGA removes excess sugar from the body through the urine and provides cardiovascular benefits.

#### WHEN IT SHOULD NOT BE USED:

Do not take FORXIGA if you:

- are allergic to dapagliflozin or any of the nonmedicinal ingredients listed below.
- have type 1 diabetes (a disease in which your body does not produce any insulin).

- have diabetic ketoacidosis (DKA, a complication of diabetes) or a history of DKA.
- have severe kidney problems or you are on dialysis.
- have severe liver disease.
- are pregnant or planning to become pregnant; it is not known if FORXIGA will harm your unborn baby. Talk to 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 FORXIGA will pass into your breast milk. Talk to your doctor if you would like to breast-feed.

#### WHAT THE MEDICINAL INGREDIENT IS:

Dapagliflozin (as dapagliflozin propanediol monohydrate).

#### WHAT THE NONMEDICINAL INGREDIENTS ARE:

Anhydrous lactose, crospovidone, magnesium stearate, microcrystalline cellulose, silicon dioxide. In addition, the film coating contains the following inactive ingredients: polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide and yellow iron oxide.

#### WHAT DOSAGE FORMS IT COMES IN:

Tablets 5 mg and 10 mg.

### WARNINGS AND PRECAUTIONS

#### **Serious Warnings and Precautions**

- Diabetic ketoacidosis (DKA) in patients with type 2 diabetes mellitus (T2DM), is a serious and life-threatening condition that requires urgent hospitalization. DKA has been reported in patients with T2DM with normal or high blood sugar levels who are treated with FORXIGA 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 FORXIGA 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 FORXIGA if you have:

- DKA or a history of DKA
- type 1 diabetes.

#### **BEFORE you use FORXIGA talk to your doctor or pharmacist if you:**

- have type 1 diabetes (your body does not produce any insulin). FORXIGA 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 illness;
- have a history of diabetic ketoacidosis (DKA).
- are older than 65 years of age
- have or have had any kidney problems
- have or have had any cases of liver disease
- have heart disease or low blood pressure
- are taking a medicine for high blood pressure or taking a water pill (used to remove excess water from the body)
- are taking medicines to lower your blood sugar such as glyburide, glimepiride or glimepiride (sulfonylureas) or insulin. Taking FORXIGA with any of these medicines can increase the risk of having low blood sugar (hypoglycemia)
- have intolerance to some milk sugars. FORXIGA tablets contain lactose
- often get urinary tract infections

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

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

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

FORXIGA 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.

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

FORXIGA may cause necrotizing fasciitis of the perineum (area between and around the anus and genitals). This is a rare but serious and potentially life-threatening infection that can affect both men and women. It is also known as Fournier's gangrene and requires urgent treatment. If you experience tenderness, redness or swelling of the genitals or the area from the genitals to the rectum, especially if you also have a fever or are feeling very weak, tired, or uncomfortable, seek medical attention immediately. These may be signs of Fournier's gangrene.

**Driving and using machines:** FORXIGA 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.

### Drugs that may interact with FORXIGA include:

- medicines you take for diabetes, especially sulfonylurea medications or insulin. Low blood sugar (hypoglycemia) may occur if you already take another medication to treat diabetes. Discuss with your doctor how much of each medicine to take.

## PROPER USE OF THIS MEDICATION

Follow the directions given to you by your doctor.

### Take FORXIGA:

- once a day
- at any time of the day
- by mouth
- with or without food

Swallow whole. Do not cut or divide tablets.

### USUAL ADULT DOSE:

#### Patients with Type 2 Diabetes Mellitus (T2DM)

Your dosage depends on your medical condition and response to treatment.

**To control your blood sugar:** the recommended adult starting dose is one 5 mg tablet a day. Your doctor may increase your dose to one 10 mg tablet, if needed.

**To reduce your risk of hospitalization due to heart failure:** the recommended adult dose is one 10 mg tablet a day.

### Heart Failure

**Recommended adult starting dose for patients with heart failure:** one 10 mg tablet a day.

### 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 FORXIGA, take it as soon as you remember. If you do not remember until it is almost time for your next dose, skip the missed dose and go back to your regular schedule. 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 FORXIGA. 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
- influenza
- constipation
- diarrhea
- nausea
- back pain
- pain in the arms, legs, hands or feet
- headache
- rash

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

FORXIGA can cause abnormal blood test results. Your doctor will decide when to perform blood tests. They may check kidney function, blood fat levels (Low Density Lipoprotein cholesterol or LDL-C) and amount of red blood cells in your blood (hematocrit).

Diabetic Ketoacidosis (DKA) in patients with T2DM, 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 in the table below under DKA, even if your blood sugar levels are normal.

## SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency / Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Common	<b>Urinary tract infection:</b> pain, difficulty or increased need to urinate		X	
	<b>Yeast infection of vagina:</b> severe itching, burning, soreness, irritation, and a whitish or whitish-gray cottage cheese-like discharge	X		

## SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency / Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Uncommon	<b>Yeast infection of penis:</b> red, swollen, itchy head of penis; thick, lumpy discharge under foreskin; unpleasant odour; difficulty retracting foreskin; pain passing urine or during sex	X		
	<b>Volume depletion (loss of needed fluids from the body; dehydration):</b> dry or sticky mouth, headache, dizziness or urinating less often than normal		X	
	<b>Low blood pressure:</b> dizziness, fainting, lightheadedness; may occur when you go from lying to sitting to standing up		X	
	<b>Low blood sugar (hypoglycemia) in patients with T2DM:</b> shaking, sweating, rapid heartbeat, change in vision, hunger, headache and change in mood		X	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Frequency / Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Rare	<b>Diabetic ketoacidosis (DKA) in patients with T2DM:</b> 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
	<b>Kidney problems:</b> any change in the amount, frequency or colour (pale or dark) of urine		X	
	<b>Fournier's gangrene (a serious infection affecting soft tissue around the groin):</b> pain or tenderness, redness of the skin, or swelling in the genital or perineal area, with or without fever or feeling very weak, tired, or uncomfortable			X

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Frequency / Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Very rare	<b>Acute kidney infection:</b> painful, urgent or frequent urination, lower back (flank) pain, fever or chills, cloudy or foul smelling urine, blood in your urine			X
	<b>Severe infection that spreads from urinary tract throughout body (sepsis):</b> fever or low body temperature, chills, rapid breathing, rapid heartbeat, pain with urination, difficulty urinating, frequent urination			X
	<b>Inflammation of the pancreas (pancreatitis):</b> severe stomach pain that lasts and gets worse when you lie down, nausea, vomiting		X	

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

### Reporting Side Effects

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

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

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

### HOW TO STORE IT

Store at room temperature (15 to 30 °C).

Keep FORXIGA out of the reach and sight of children.

### MORE INFORMATION

NOTE: This CONSUMER INFORMATION 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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