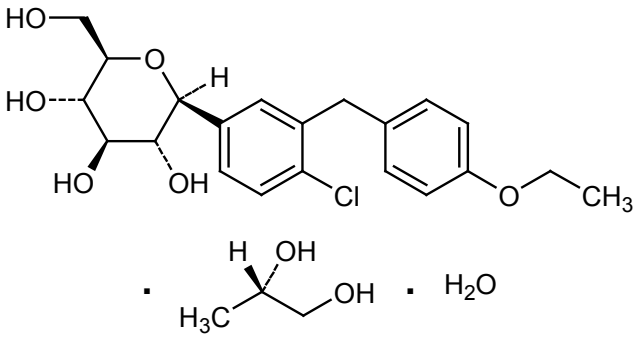
FORXIGA

dapagliflozin propanediol monohydrate

PRODUCT INFORMATION

NAME OF THE MEDICINE

The active ingredient in FORXIGA is dapagliflozin propanediol monohydrate, an orally-active inhibitor of the human renal sodium-glucose co-transporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin is described chemically as (1*S*)-1,5-Anhydro-1-C-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-D-glucitol, (*S*)-propylene glycol, monohydrate. The empirical formula is $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$ and the molecular weight is 502.98. The structural formula is:



CAS Number: 960404-48-2

DESCRIPTION

Each film-coated tablet of FORXIGA contains 10 mg of dapagliflozin (as dapagliflozin propanediol monohydrate) and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, crospovidone, silicon dioxide, magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc and yellow iron oxide.

PHARMACOLOGY

Pharmacological actions

Mechanism of action

Dapagliflozin is a reversible competitive inhibitor of sodium glucose co-transporter 2 (SGLT2) with nanomolar potency that improves glycemic control in patients with type 2 diabetes mellitus by reducing renal glucose reabsorption leading to urinary glucose excretion (glucuresis). FORXIGA is orally available and requires once daily dosing.

SGLT2 is selectively expressed in the kidney with no expression detected in more than 70 other tissues including liver, skeletal muscle, adipose tissue, breast, bladder and brain. SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Despite the presence of hyperglycemia in type 2 diabetes mellitus, reabsorption of filtered glucose continues. Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24 hour dosing interval, and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Thus, in healthy subjects with normal glucose, dapagliflozin has a low propensity to cause hypoglycemia. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycemia. Dapagliflozin acts independently of insulin secretion and insulin action. Over time, improvement in beta cell function (HOMA-2) has been observed in clinical studies with dapagliflozin.

Urinary glucose excretion (glucuresis) induced by dapagliflozin is associated with caloric loss and reduction in weight. The majority of the weight reduction was body fat loss, including visceral fat rather than lean tissue or fluid loss as demonstrated by dual energy X-ray absorptiometry (DXA) and magnetic resonance imaging.

Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is approximately 1000 - 3000 times more selective for SGLT2 vs. SGLT1, the major transporter in the gut responsible for glucose absorption.

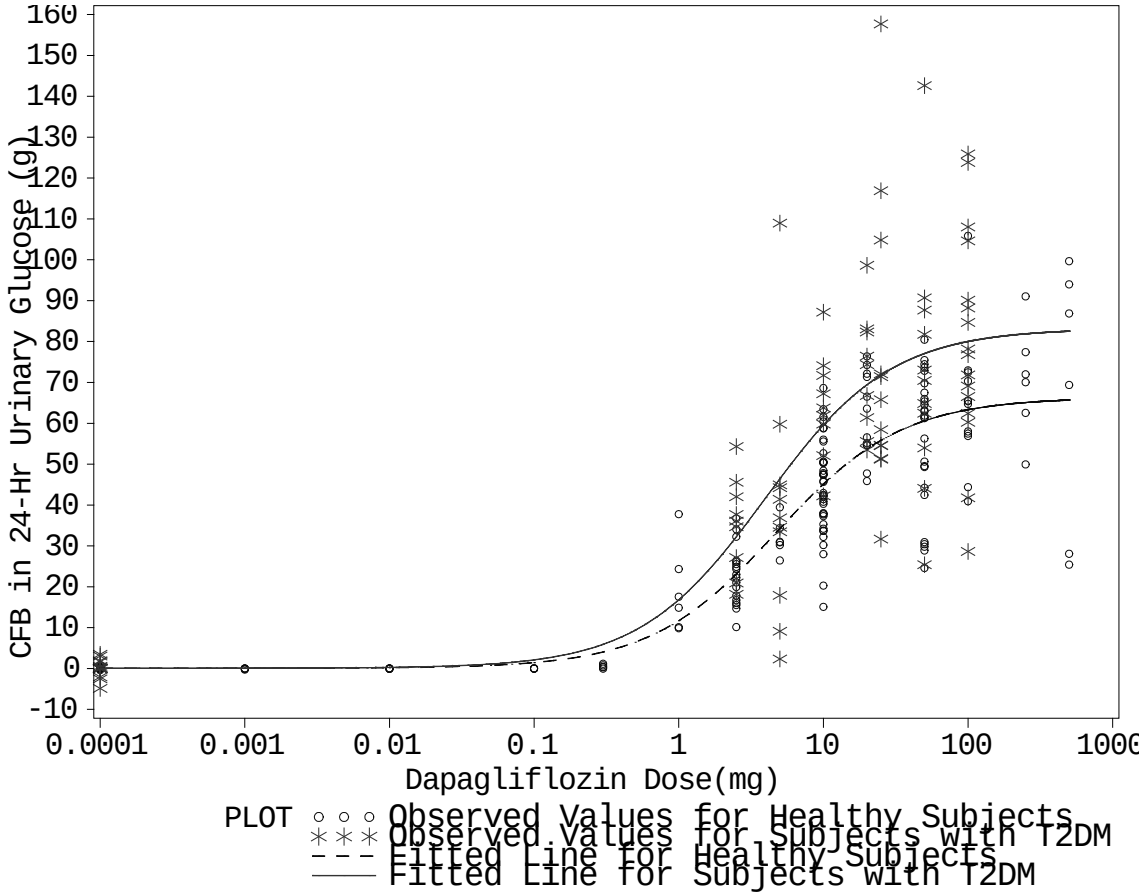
Pharmacodynamic effects

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following the administration of dapagliflozin (Figure 1). Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day) at a dapagliflozin dose of 10 mg/day in patients with type 2 diabetes mellitus for 12 weeks. This glucose elimination rate approached the maximum glucose excretion observed at 20 mg/day dose of dapagliflozin. Evidence of sustained glucose excretion was seen in patients with type 2 diabetes mellitus given dapagliflozin 10mg/day for up to 2 years.

This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume. Urinary volume increases in patients with type 2 diabetes mellitus treated with 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 µmol/L.

Figure 1 **Scatter Plot and Fitted Line of Change from Baseline in 24-hr Urinary Glucose Amount *vs* Dapagliflozin Dose in Healthy Subjects and Subjects with T2DM (Semi-Log Plot)**



Cardiac Electrophysiology

Dapagliflozin was not associated with clinically meaningful prolongation of QTc interval at daily doses up to 150 mg (15 times the recommended dose) in a study of healthy subjects. In addition, no clinically meaningful effect on QTc interval was observed following single doses of up to 500 mg (50 times the recommended dose) dapagliflozin in healthy subjects.

Pharmacokinetics

Absorption

Dapagliflozin was rapidly and well absorbed after oral administration and can be administered with or without food. Maximum dapagliflozin plasma concentrations (Cmax) were usually attained within 2 hours after administration in the fasted state. The Cmax and AUC values increased proportional to the increment in dapagliflozin dose. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Food had relatively modest effects on the pharmacokinetics of dapagliflozin in healthy subjects. Administration with a high-fat meal decreased

dapagliflozin Cmax by up to 50% and prolonged Tmax 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 (eg, renal or hepatic impairment).

Metabolism

Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide. Dapagliflozin 3-O-glucuronide, with a molar plasma AUC 52% higher than that of dapagliflozin itself at the clinical dose, is an inactive metabolite and does 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.

Elimination

Dapagliflozin and related metabolites are primarily eliminated via urinary excretion, of which less than 2% is unchanged dapagliflozin. After oral administration of 50 mg [14C]-dapagliflozin dose, 96% was recovered, 75% in urine and 21% in faeces. In faeces, approximately 15% of the dose was excreted as parent drug. The mean plasma terminal half-life (t1/2) for dapagliflozin was 12.9 hours following a single oral dose of FORXIGA 10 mg to healthy subjects.

Special Populations

No dosages adjustments based on pharmacokinetic analyses are recommended for normal-to-mild renal impairment (eGFR ≥ 60 mL/min/1.73 m^2 or CrCl ≥ 60 mL/min), mild, or moderate hepatic impairment, age, gender, race and body weight.

Renal Impairment

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

Hepatic Impairment

For dosing recommendations for patients with moderate hepatic impairment (see DOSAGE and ADMINISTRATION). A single dose (10 mg) dapagliflozin clinical

pharmacology study was conducted in patients with mild, moderate or severe hepatic impairment (Child-Pugh classes A, B, and C, respectively) and healthy matched controls in order to compare the pharmacokinetic characteristics of dapagliflozin between these populations. There were no differences in the protein binding of dapagliflozin between hepatic impairment groups or compared to healthy subjects. In patients with mild or moderate hepatic impairment mean Cmax and AUC of dapagliflozin were up to 12% and 36% higher, respectively, compared to healthy matched control subjects. These differences were not considered to be clinically meaningful and no dose adjustment from the proposed usual dose of 10 mg once daily for dapagliflozin is proposed for these populations. In patients with severe hepatic impairment (Child-Pugh class C) mean Cmax and AUC of dapagliflozin were up to 40% and 67% higher than matched healthy controls, respectively.

Age

No dosage adjustment for dapagliflozin is recommended on the basis of age. The effect of age (young: ≥18 to <40 years [n=105] and elderly: ≥ 65 years [n=224]) was evaluated as a covariate in a population pharmacokinetic model and compared to patients ≥40 to < 65 years using data from healthy subject and patient studies). The mean dapagliflozin systemic exposure (AUC) in young patients was estimated to be 10.4% lower than in the reference group [90% CI: 87.9, 92.2%] and 25% higher in elderly patients compared to the reference group [90% CI: 123, 129%]. However, an increased exposure due to age-related decrease in renal function can be expected. There are insufficient data to draw conclusions regarding exposure in patients > 70 years old.

Paediatric and Adolescent

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

Gender

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

Race

No dosage adjustment from the dapagliflozin dose of 10 mg once daily is recommended on the basis of race. Race (white, black [African descent] or Asian) was evaluated as a covariate in a population pharmacokinetic model using data from healthy subject and patient studies. Differences in systemic exposures between these races were small. Compared to whites (n=1147), Asian subjects (n=47) had no difference in estimated mean dapagliflozin systemic exposures [90% CI range 3.7% lower, 1% higher]. Compared to whites, black (African descent) 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 patient studies, systemic exposures in high body weight subjects (≥120 kg, n=91) were estimated to be 78.3% [90% CI: 78.2, 83.2%] of those of reference subjects with body weight between 75 and 100 kg. This difference is considered to be small, therefore, no

dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in type 2 diabetes mellitus patients with high body weight (≥120 kg) is recommended.

Subjects with low body weights (<50 kg) were not well represented in the healthy subject and patient studies used in the population pharmacokinetic analysis. Therefore, 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. This difference is considered to be small and based on these findings no dose adjustment from the proposed dose of 10 mg dapagliflozin once daily in type 2 diabetes mellitus patients with low body weight (<50 kg) is recommended.

CLINICAL TRIALS

Exposure to dapagliflozin is limited to the clinical trial program as there is no post-marketing experience at this stage. In relation to the proposed 10 mg dosage, many of the studies contain multiple dosage regimens. In the 40 included studies, 4922 subjects received at least one dose of dapagliflozin and of these 2000 received at least one 10 mg dose in a phase 2b or 3 study. In the 24 week short-term placebo-controlled studies, 1193 subjects received 10 mg of dapagliflozin with 682 of these continuing treatment in longer term extensions.

In the pivotal phase 3 studies, FORXIGA has been studied as monotherapy and in combination with metformin, glimepiride, and insulin. A total of 5693 patients with type 2 diabetes mellitus were treated in 11, double-blind, controlled clinical studies conducted to evaluate the safety and glycemic efficacy of FORXIGA; 3939 patients in these studies were treated with FORXIGA up to a maximum duration of exposure of 102 weeks. The primary endpoint was reduction in HbA1c levels in 10 studies and decrease in body weight in 1 study. Ten studies had a treatment period of 24 weeks duration and one study was 52 weeks in duration. Of the ten 24-week studies, 5 studies had long-term extensions ranging from 24 to 78 weeks (up to total study duration of 102 weeks). Across the 11 clinical studies, the mean age was 56 years (18-92), and the mean duration of diabetes ranged from 1.4 to 16.9 years. Fifty-one percent (51%) of patients were men, 84% were white, 10% were Asian, 3% were black (African descent), and 3% were of other racial groups. Eighty percent (80%) of patients had a BMI of $\geq$27 kg/m^2. FORXIGA has also been studied in patients with mild (51% of the population studied) to moderate (12% of the population studied) renal impairment.

Treatment with FORXIGA as monotherapy and in combination with metformin, glimepiride, and insulin produced clinically relevant and statistically significant improvements in mean change from baseline at week 24 in HbA1c, fasting plasma glucose (FPG), and 2-hour post-prandial glucose (PPG)(where measured), compared to control. These clinically relevant glycemic effects were sustained in long-term extensions up to 102 weeks. HbA1c reductions were seen across subgroups including gender, age, race, duration of disease, and baseline BMI. Additionally at week 24, clinically relevant and statistically significant improvements in mean changes from baseline in body weight, a secondary endpoint, were seen with FORXIGA combination treatments compared to control (see Tables 2-6). Body weight reductions were sustained in long-term extensions up to 102 weeks. In a dedicated clinical study,

decrease in weight, a primary efficacy endpoint, was mainly attributable to a reduction in body fat mass as measured by DXA.

FORXIGA was evaluated at 10mg once daily in 9 of 11 double-blind studies. Doses of dapagliflozin 2.5 mg and dapagliflozin 5 mg were also evaluated, 2.5 mg was not consistently effective for glycemic control and 10 mg had better numerical efficacy and comparable safety to dapagliflozin 5 mg.

Monotherapy

A total of 840 treatment-naive patients with inadequately controlled type 2 diabetes participated in two placebo-controlled studies to evaluate the efficacy and safety of monotherapy with FORXIGA. In both studies, treatment-naive patients were defined as either never having received diabetes medication or having had such for less than 24 weeks since the diagnosis of diabetes, not for more than 14 days during the 12 weeks prior to enrolment, and not at all during the 4 weeks prior to enrolment.

In one monotherapy study, a total of 558 patients with inadequately controlled diabetes participated in a 24-week study with a 78-week controlled, blinded extension period. Following a 2-week diet and exercise placebo lead-in period, 485 patients with HbA1c $\geq$7% to $\leq$10% were randomized to dapagliflozin 2.5 mg, dapagliflozin 5 mg, or FORXIGA 10 mg once daily in either the morning (QAM, main cohort) or evening (QPM), or placebo in the morning only.

At week 24, treatment with FORXIGA 10 mg QAM provided significant improvements in HbA1c and FPG compared with placebo (Table 1, Figure 2). Overall, the PM administration of dapagliflozin had a comparable safety and efficacy profile as dapagliflozin administered in the AM. Adjusted mean change from baseline in HbA1c, and FPG was -0.63% and -1.5 mmol/L, respectively, at week 102 in the QAM group, for patients treated with FORXIGA 10mg, and -0.18% and was -0.3 mmol/L, respectively, for patients treated with placebo based on the longitudinal repeated measures analysis excluding data after rescue.

The proportion of patients in the main cohort who were rescued or discontinued for lack of glycemic control at week 24 (adjusted for baseline HbA1c) was higher on placebo (12.0%) than on FORXIGA 10mg (0.0%).

Table 1: 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 10 mg N=70†	Placebo N=75†
HbA1c (%)		
Baseline (mean)	8.01	7.79
Change from baseline (adjusted mean‡)	−0.89	−0.23
Difference from placebo (adjusted mean‡) (95% CI)	−0.66§ (−0.96, −0.36)	
Percent of patients achieving HbA1c <7% adjusted for baseline	50.8%¶	31.6%
Change from baseline in HbA1c in patients with baseline HbA1c ≥9% (adjusted mean‡)	−2.04¶ (N=14)	0.19 (N=5)
FPG (mmol/L)		
Baseline (mean)	9.3	8.9
Change from baseline (adjusted mean‡)	−1.6	−0.2
Difference from placebo (adjusted mean‡) (95% CI)	−1.4§ (−2.0, −0.8)	
Body Weight (kg)		
Baseline (mean)	94.13	88.77
Change from baseline (adjusted mean‡)	−3.16	−2.19
Difference from placebo (adjusted mean‡) ^ (95% CI)	−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.

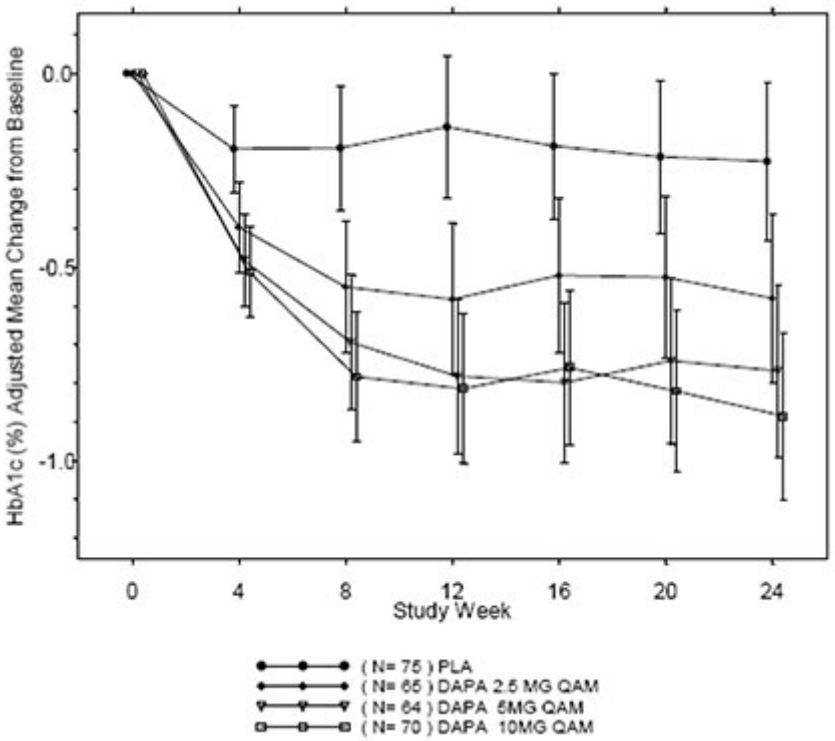
‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001 vs. placebo.

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

^ Not statistically significant.

Figure 2: Adjusted Mean Change from Baseline Over Time (LOCF) in HbA1c in a 24-Week Placebo-Controlled Study of FORXIGA Monotherapy in Patients with Type 2 Diabetes (Group 1 AM Doses)



Error bars represent 95% confidence intervals for the adjusted mean change from baseline

There was a long term observational extension to this study: the results after 99-102 weeks treatment suggested a lessening of benefit despite dropouts: the differences from placebo for the 5 mg and 10 mg groups of 0.59% and 0.45% are similar to those observed at 24 weeks but were derived from 16 and 21 subjects, respectively, remaining in follow-up. The majority of subjects had discontinued progressively for lack of glycaemic control or for need for rescue therapy. By week 102, more patients on placebo (44.0%) required rescue therapy than patients on FORXIGA 10 mg (34.0%). Rescue therapy criteria became stricter over time: after week 24 to week 50: HbA1c >8%; after week 50 to week 76: HbA1c >7.5%; after week 76 to week 102 (excluding week 102): HbA1c >7%.

Combination Therapy

FORXIGA was studied as add-on to metformin, add-on to a sulfonylurea (glimepiride), and add-on to insulin (with or without other antidiabetic therapies).

Combination Therapy with Metformin

Four studies were conducted in combination with metformin therapy: two studies evaluated FORXIGA added to metformin as initial combination therapy, one study evaluated the effect of FORXIGA added to metformin in patients already on metformin, and one study evaluated the effect of FORXIGA added to metformin vs. sulfonylurea.

Initial Combination Therapy with Metformin

A total of 1,244 treatment-naive patients with inadequately controlled type 2 diabetes (HbA1c $\geq$ 7.5% and $\leq$ 12%) participated in two active-controlled studies of 24-weeks duration to evaluate the efficacy and safety of initial therapy with dapagliflozin 5 mg or FORXIGA 10 mg in combination with metformin extended-release formulation (XR). In both studies, treatment-naive patients were defined as either never having received diabetes medication or having had such for less than 24 weeks since the diagnosis of diabetes, not for more than 14 days during the 12 weeks prior to enrolment, and not at all during the 4 weeks prior to enrolment.

In one study, 641 patients were randomized to one of three treatment arms following a 1-week lead-in period: FORXIGA 10 mg plus metformin XR (up to 2000 mg per day), FORXIGA 10 mg plus placebo, or metformin XR (up to 2000 mg per day) plus placebo. Metformin dose was up-titrated weekly in 500 mg increments, as tolerated, with the maximum and median dose achieved being 2000 mg.

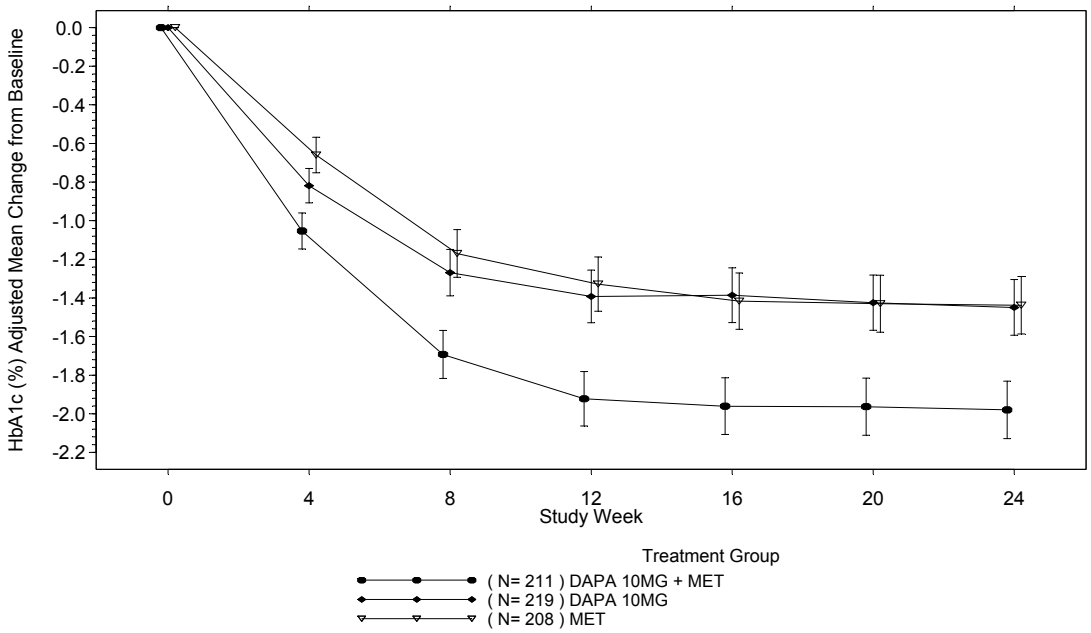
The combination treatment of FORXIGA 10 mg plus metformin provided significant improvements in HbA1c and FPG, compared with either of the monotherapy treatments and significant improvements in body weight compared with metformin alone. (Table 2, Figures 3 and 4). FORXIGA 10 mg as monotherapy also provided significant improvements in FPG and body weight compared with metformin alone and was non-inferior to metformin monotherapy in lowering HbA1c. The proportion of patients who were rescued or discontinued for lack of glycemic control during the 24 week double-blind treatment period (adjusted for baseline HbA1c) was higher on treatment with metformin plus placebo (13.5%) than on FORXIGA 10 mg plus placebo and FORXIGA 10 mg plus metformin (7.8%, and 1.4%).

Table 2: Results at Week 24 (LOCF[*]) in an Active-Controlled Study of FORXIGA Initial Combination Therapy with Metformin XR

Efficacy Parameter	FORXIGA 10 mg + Metformin XR N=211[†]	FORXIGA 10 mg N=219[†]	Metformin XR N=208[†]
HbA1c (%)			
Baseline (mean)	9.10	9.03	9.03
Change from baseline (adjusted mean[‡])	−1.98	−1.45	−1.44
Difference from FORXIGA (adjusted mean[‡]) (95% CI)	−0.53[§] (−0.74, −0.32)		
Difference from metformin (adjusted mean[‡]) (95% CI)	−0.54[§] (−0.75, −0.33)	−0.01[¶] (−0.22, 0.20)	
Percent of patients achieving HbA1c <7% adjusted for baseline	46.6%[#]	31.7%	35.2%
Change from baseline in HbA1c in patients with baseline HbA1c ≥9% (adjusted mean[‡)]	−2.59[#]	−2.14	−2.05
FPG (mmol/L)			
Baseline (mean)	10.5	11.0	10.5
Change from baseline (adjusted mean[‡])	−3.4	−2.6	−1.9
Difference from FORXIGA (adjusted mean[‡]) (95% CI)	−0.8[§] (−1.2, −0.4)		
Difference from metformin (adjusted mean[‡]) (95% CI)	−1.4[§] (−1.8, −1.0)	−0.6[¶] (−1.0, −0.3)	
Body Weight (kg)			
Baseline (mean)	88.56	88.53	87.24
Change from baseline (adjusted mean[‡])	−3.33	−2.73	−1.36
Difference from metformin (adjusted mean[‡]) (95% CI)	−1.97[§] (−2.64, −1.30)	−1.37[§] (−2.03, −0.71)	

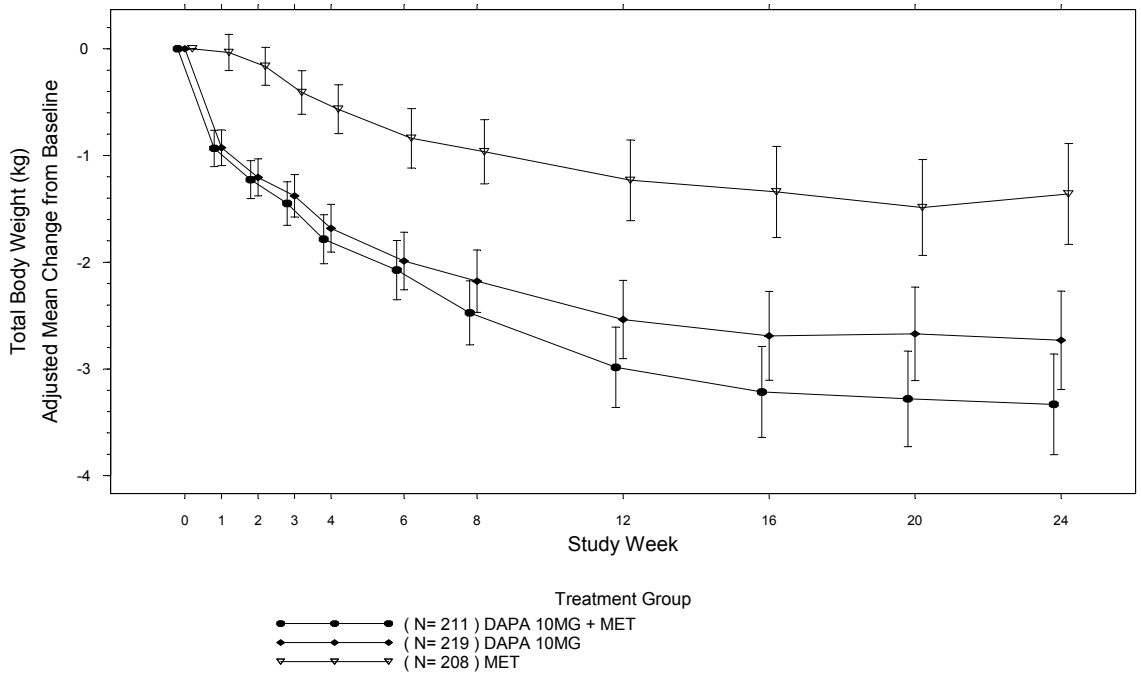
[*] LOCF: last observation (prior to rescue for rescued patients) carried forward.
[†] All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.
[‡] Least squares mean adjusted for baseline value.
[§] p-value <0.0001.
[¶] Non-inferior versus metformin.
[#] p-value <0.05.

Figure 3: Adjusted Mean Change from Baseline Over Time (LOCF[a]) in HbA1c in a 24-Week Active-Controlled Study of FORXIGA Initial Combination Therapy with Metformin XR



[a] Values in the plot represent adjusted mean and 95% confidence intervals (for Week 24 only) based on the ANCOVA model using LOCF (last observation (prior to rescue for rescued subjects) carried forward) data.

Figure 4: Adjusted Mean Change from Baseline Over Time (LOCF[a]) in Total Body Weight (kg) in a 24-Week Active-Controlled Study of FORXIGA Initial Combination Therapy with Metformin XR



[a] LOCF: last observation (prior to rescue for rescued patients) carried forward
Error bars represent 95% confidence intervals for the adjusted mean change from baseline

Add-on to Metformin

A total of 546 patients with type 2 diabetes with inadequate glycemic control (HbA1c ≥7% and ≤10%) participated in a 24-week placebo-controlled study with a 78-week controlled, blinded extension period to evaluate FORXIGA in combination with metformin. Patients on metformin at a dose of at least 1500 mg per day were randomized after completing a 2-week single-blind placebo lead-in period. Following the lead-in period, eligible patients were randomized to dapagliflozin 2.5 mg, dapagliflozin 5 mg, or FORXIGA 10 mg, or placebo in addition to their current dose of metformin.

As add-on treatment to metformin, FORXIGA 10 mg provided significant improvements in HbA1c , FPG, and body weight compared with placebo at week 24 (Table 3, Figure 3). At week 102, adjusted mean change from baseline in HbA1c (see Figure 5), FPG, and body weight was -0.78%, -1.4 mmol/L, and -2.81 kg , respectively, for patients treated with FORXIGA 10 mg plus metformin and 0.02%, -0.6 mmol/L, and -0.67 kg for patients treated with placebo plus metformin based on the longitudinal repeated measures analysis excluding data after rescue. The proportion of patients who were rescued or discontinued for lack of glycemic control during the 24 week double-blind treatment period (adjusted for baseline HbA1c) was higher in the placebo plus metformin group (15.0%) than in the FORXIGA 10 mg plus metformin group (4.4%). By

week 102, more patients on placebo plus metformin (60.1%) required rescue therapy than patients on FORXIGA 10 mg plus metformin (44.0%).

Table 3: Results of a 24-Week (LOCF*) Placebo-Controlled Study of FORXIGA in Add-On Combination with Metformin

Efficacy Parameter	FORXIGA 10 mg + Metformin N=135†	Placebo + Metformin N=137†
HbA1c (%)		
Baseline mean	7.92	8.11
Change from baseline (adjusted mean‡)	−0.84	−0.30
Difference from placebo (adjusted mean‡) (95% CI)	−0.54§ (−0.74, −0.34)	
Percent of patients achieving HbA1c <7% adjusted for baseline	40.6%¶	25.9%
Change from baseline in HbA1c in patients with baseline HbA1c ≥9% (adjusted mean‡)	−1.32¶ (N= 18)	−0.53 (N= 22)
FPG (mmol/L)		
Baseline mean	8.7	9.2
Change from baseline at week 24 (adjusted mean‡)	−1.3	−0.3
Difference from placebo (adjusted mean‡) (95% CI)	−1.0§ (−1.4, −0.6)	
Change from baseline at week 1 (adjusted mean‡)	−0.9§ (N=115)	0.1 (N=126)
Body Weight (kg)		
Baseline mean	86.28	87.74
Change from baseline (adjusted mean‡)	−2.86	−0.89
Difference from placebo (adjusted mean‡) (95% CI)	−1.97§ (−2.63, −1.31)	

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

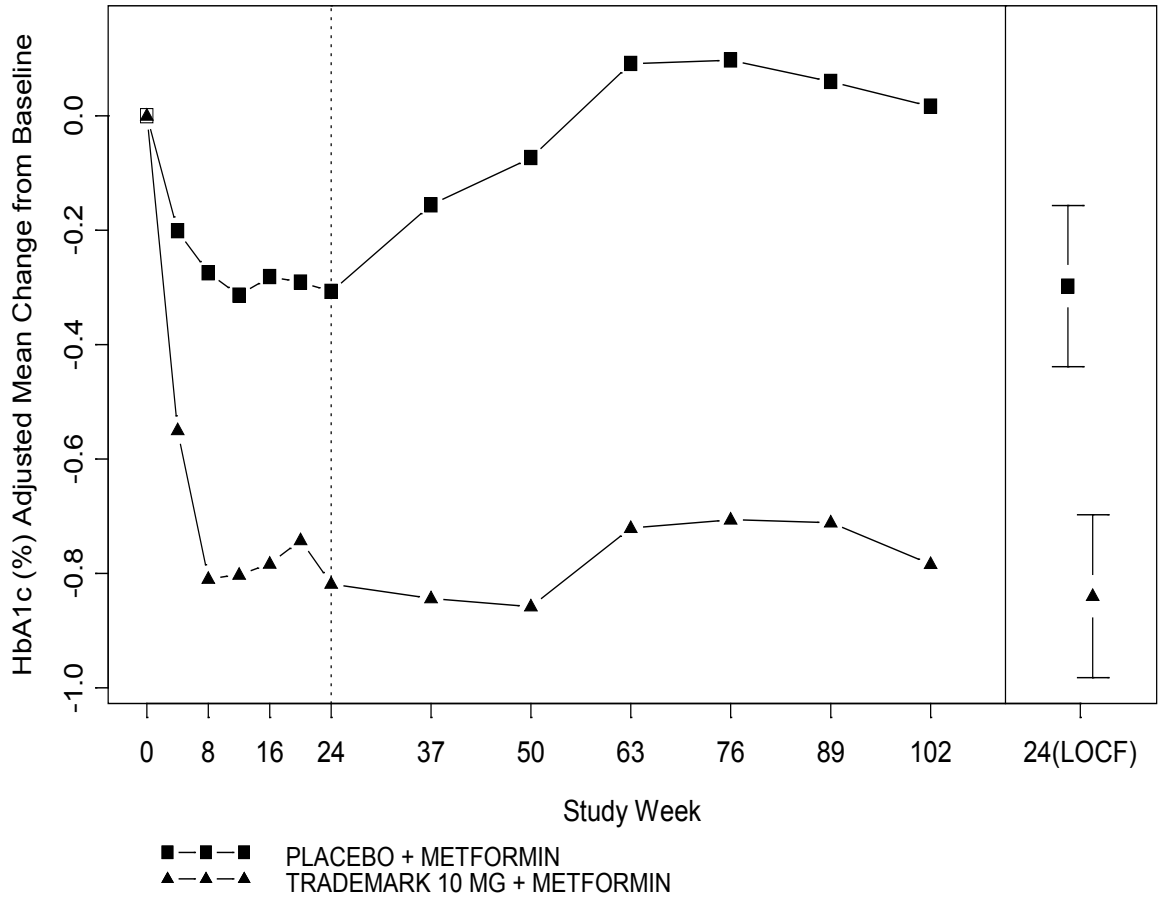
† All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.

‡ Least squares mean adjusted for baseline value.

§ p-value <0.00001 vs placebo + metformin.

¶ p-value <0.05 vs placebo + metformin.

Figure 5: Adjusted Mean Change from Baseline Over Time in HbA1c in a 102-Week Placebo-Controlled Study of FORXIGA in Combination with Metformin (Longitudinal Repeated Measures Analysis, Excluding Data after Rescue)



LOCF: Last observation (prior to rescue for rescued subjects) carried forward
Values for 24(LOCF) represent adjusted mean and 95% confidence intervals based on an ANCOVA model
Values for other weeks represent adjusted means based on a longitudinal repeated measures model

Active Glipizide Controlled Study Add-on to Metformin

A total of 816 patients with type 2 diabetes with inadequate glycemic control (HbA1c >6.5% and ≤10%) were randomized in this 52-week, 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 (a sulfonylurea) or dapagliflozin (5 mg or 2.5 mg, respectively) and were up-titrated over 18 weeks to optimal glycemic effect (FPG <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 dapagliflozin had been titrated to the maximum study dose (10 mg), versus 73% treated with glipizide (20 mg). FORXIGA led to a similar mean reduction in HbA1c from baseline to week 52 (LOCF),

compared with glipizide, thus demonstrating non-inferiority (Table 4, Figures 6 and 7). FORXIGA treatment led to a significant mean reduction in body weight from baseline to week 52 (LOCF) compared with a mean increase in body weight in the glipizide group.

The proportion of patients who discontinued for lack of glycemic control (adjusted for baseline HbA1c) was higher on glipizide plus metformin (3.7%) than on FORXIGA plus metformin (0.3%). A significantly lower proportion of patients on FORXIGA (3.5%) experienced at least one event of hypoglycemia over 52 weeks of treatment, compared to glipizide (40.8%).

Table 4: 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†	Glipizide +Metformin N=401†
HbA1c (%)		
Baseline (mean)	7.69	7.74
Change from baseline (adjusted mean‡)	−0.52	−0.52
Difference from Glipizide+Metformin (adjusted mean‡)	0.00¶	
(95% CI)	(−0.11, 0.11)	
Body Weight (kg)		
Baseline (mean)	88.44	87.60
Change from baseline (adjusted mean‡)	−3.22	1.44
Difference from Glipizide+Metformin (adjusted mean‡)	−4.65§	
(95% CI)	(−5.14, −4.17)	
Percent of patients achieving weight loss >5% (adjusted) (95%CI)	33.3%§ (28.7, 37.9)	2.5% (1.0, 4.0)

*LOCF: last observation carried forward.

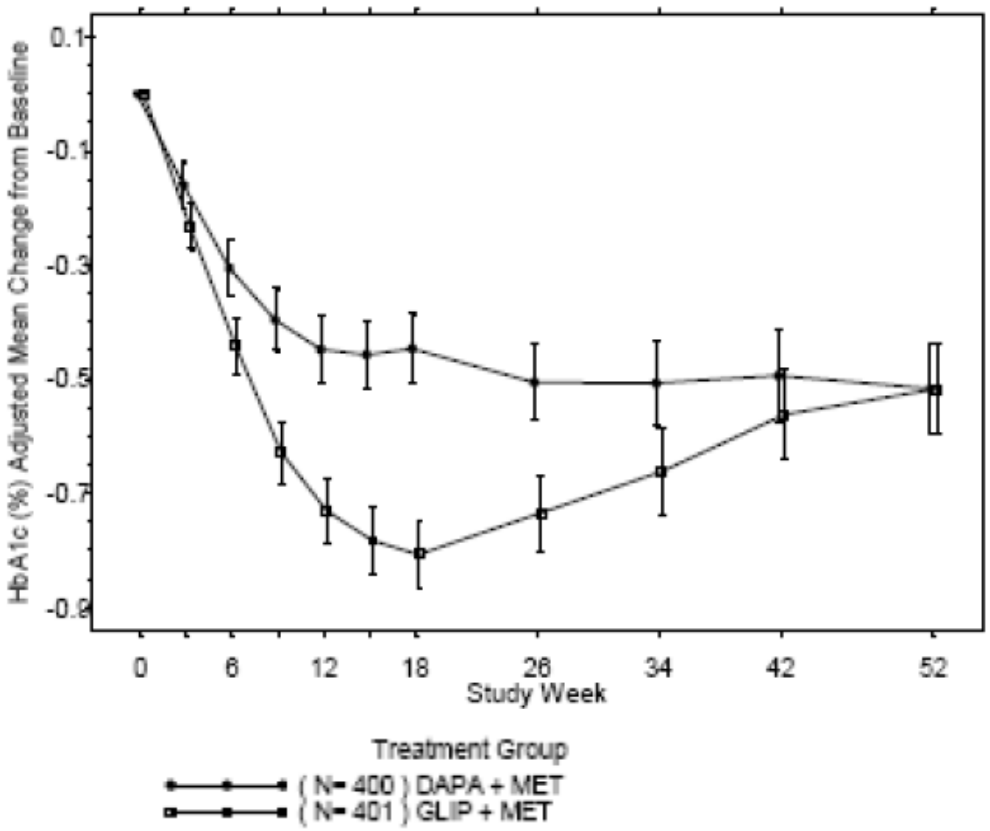
† Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.

‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001.

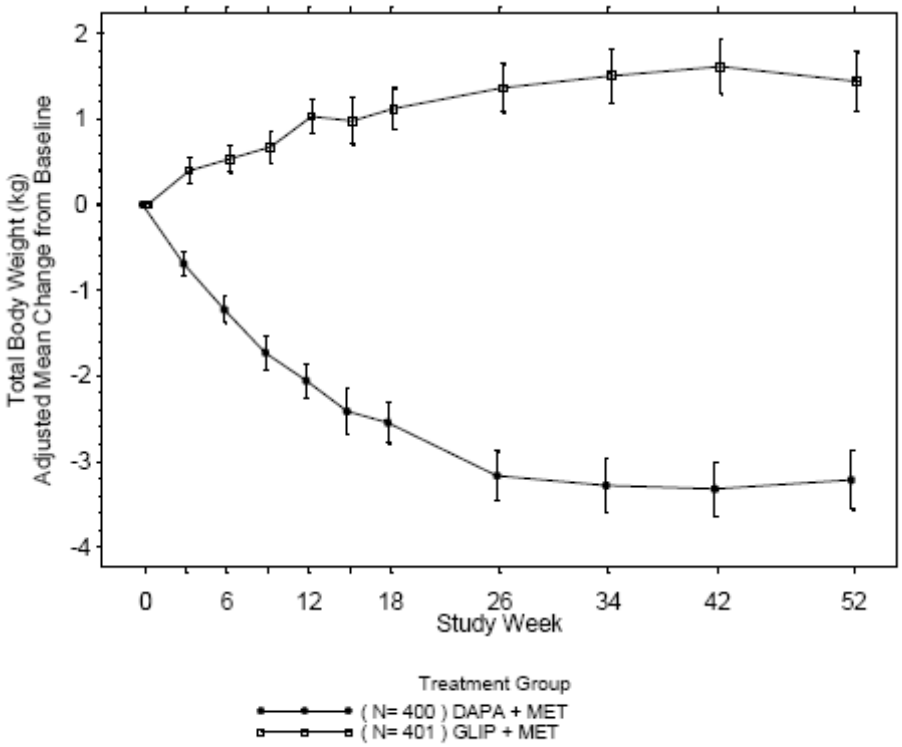
¶ non-inferior to glipizide + metformin

Figure 6: Adjusted mean change from baseline over time in HbA1c (%) (LOCF) for the 52-week short-term treatment period in an Active-Controlled Study comparing FORXIGA to Glipizide as Add-on to Metformin



Error bars represent 95% confidence intervals for the adjusted mean change from baseline

Figure 7: Adjusted mean change from baseline over time in Body Weight (LOCF) for the 52-week short-term treatment period in an Active-Controlled Study comparing FORXIGA to Glipizide as Add-on to Metformin



Error bars represent 95% confidence intervals for the adjusted mean change from baseline.

Combination therapy with Other Anti-Diabetic Agents

Add-on Combination Therapy with a Sulfonylurea

A total of 597 patients with type 2 diabetes and inadequate glycemic control (HbA1c ≥7% and ≤10%) were randomized in this 24-week, placebo-controlled study with a 24-week extension period to evaluate FORXIGA in combination with glimepiride (a sulfonylurea).

Patients on at least half the maximum recommended dose of glimepiride as monotherapy (4 mg) for at least 8 weeks lead-in were randomized to dapagliflozin 2.5 mg, dapagliflozin 5 mg, or FORXIGA 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.

In combination with glimepiride, FORXIGA 10mg provided significant improvement in HbA1c, FPG, 2-hour PPG, and body weight compared with placebo plus glimepiride at week 24 (Table 5, Figure 8). At week 48, adjusted mean change from baseline in HbA1c, FPG, and body weight were -0.73%, -1.6 mmol/L, and -2.41 kg, respectively, for patients treated with FORXIGA 10mg plus glimepiride and -0.04%, 0.1 mmol/L, and -0.77 kg for patients treated with placebo plus glimepiride at week 48 based on the longitudinal repeated measures analysis excluding data after rescue.

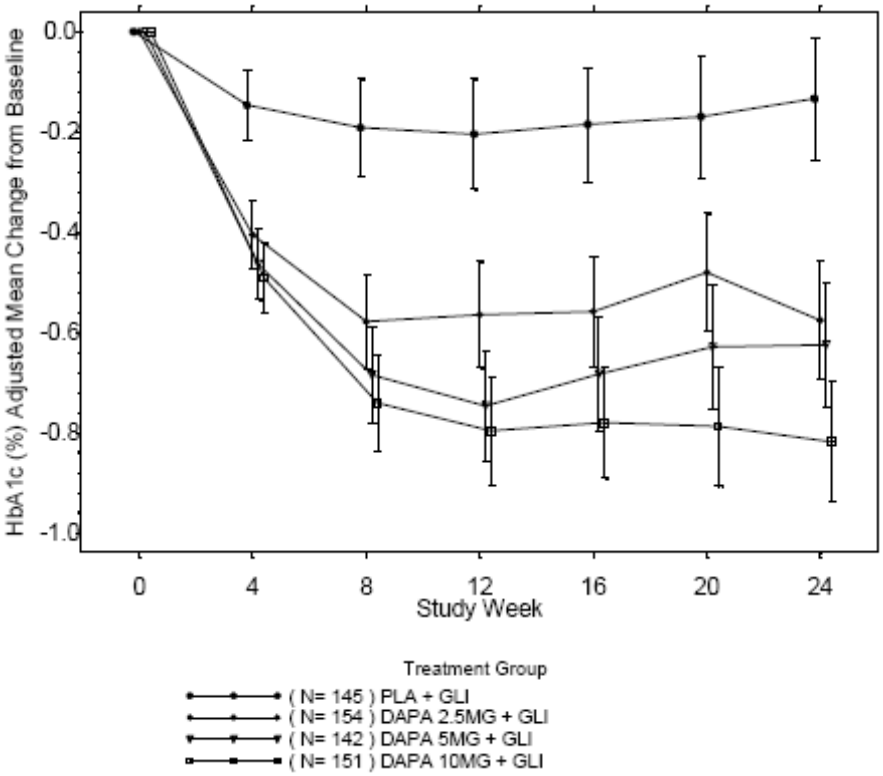
The proportion of patients who were rescued or discontinued for lack of glycemic control (adjusted for baseline HbA1c) was higher on placebo plus glimepiride (16.2%) than on FORXIGA 10 mg plus glimepiride (2.0%). By week 48, more patients on placebo plus glimepiride (53.1%) required rescue therapy than patients on FORXIGA 10 mg plus glimepiride (17.9%).

Table 5: Results of 24-Week (LOCF*) Placebo-Controlled Study of FORXIGA in Combination with Sulfonylurea (Glimepiride)

Efficacy Parameter	FORXIGA 10 mg + glimepiride	Placebo + glimepiride
Intent-to-Treat Population	N=151[†]	N=145[†]
HbA1c (%)		
Baseline (mean)	8.07	8.15
Change from baseline (adjusted mean[‡])	−0.82	−0.13
Difference from placebo + glimepiride (adjusted mean[‡]) (95% CI)	−0.68[§] (−0.86, −0.51)	
Percent of patients achieving HbA1c <7% adjusted for baseline	31.7%[§]	13.0%
FPG (mmol/L)		
Baseline (mean)	9.6	9.6
Change from baseline (adjusted mean[‡])	-1.6	-0.1
Difference from placebo + glimepiride (adjusted mean[‡]) (95% CI)	−1.5[§] (−1.9, −1.1)	
2-hour PPG[¶] (mmol/L)		
Baseline (mean)	8.7	8.8
Change from baseline (adjusted mean[‡])	-1.9	-0.3
Difference from placebo + glimepiride (adjusted mean[‡]) (95% CI)	−1.6[§] (−2.3, −0.9)	
Body Weight (kg)		
Baseline (mean)	80.56	80.94
Change from baseline (adjusted mean[‡])	−2.26	−0.72
Difference from placebo + glimepiride (adjusted mean[‡]) (95% CI)	−1.54[§] (−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.
¶ 2-hour PPG level as a response to a 75-gram oral glucose tolerance test (OGTT).

Figure 8: Adjusted Mean Change from Baseline Over Time (LOCF) in HbA1c in a Placebo-Controlled Study of FORXIGA in Combination with a Sulfonylurea (Glimepiride)



Error bars represent 95% confidence intervals for the adjusted mean change from baseline

Add-on Combination Therapy with Insulin

A total of 808 patients with type 2 diabetes who have inadequate glycemic control (HbA1c ≥7.5% and ≤10.5%) were randomized in this 24-week, placebo-controlled study with a 24-week extension period 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 OADs including metformin were randomized after completing a 2-week enrollment period to receive dapagliflozin 2.5 mg, dapagliflozin 5 mg, or FORXIGA 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. Dose modifications of blinded study medication or OAD(s) were not allowed during the treatment phase, with the exception of decreasing OAD(s) where there were concerns over hypoglycemia after cessation of insulin therapy.

In this study, 50% of patients were on insulin monotherapy at baseline, while 50% were on 1 or 2 OADs in addition to insulin, mostly metformin alone (40%) and a smaller percentage using metformin plus a sulphonylurea (5.8%) or other combinations (4.4%). The median insulin dose was 65 units daily with 20% of subjects on > 100 units daily.

At week 24, FORXIGA 10 mg dose provided significant improvement in HbA1c, body weight, and mean insulin dose compared with placebo in combination with insulin, with or without up to 2 OADs (Table 7, Figures 10,11 and 12); the effect of FORXIGA on HbA1c was similar in patients on insulin alone and patients on insulin plus OAD. At week 48, adjusted mean change from baseline in HbA1c, FPG, and body weight was -0.93%, -1.2 mmol/L, and -1.79 kg, respectively, for patients treated with FORXIGA 10mg plus insulin and -0.43%, -0.2 mmol/L, and -0.18 kg, respectively, for patients treated with placebo at week 48 based on the longitudinal repeated measures analysis excluding data after rescue.

At week 24, a significantly higher proportion of patients on FORXIGA 10 mg could reduce the insulin dose by at least 10% compared to placebo. The proportion of patients who required up-titration of their insulin dose or discontinued due to lack of glycemic control (adjusted for baseline HbA1c) was higher on placebo plus insulin (29.2%) than on FORXIGA 10 mg plus insulin (9.7%). The insulin dose remained stable in patients treated with FORXIGA, but continued to increase (mean increase 10.5 IU from baseline) in placebo-treated patients up to 48 weeks. By week 48, more patients on placebo (41.5%) required up-titration with insulin to maintain glycemic levels than patients on FORXIGA 10 mg (15.5%).

Table 6: Results of 24-Week (LOCF*) Placebo-Controlled Study of FORXIGA in Combination with Insulin with or without up to 2 Oral Antidiabetic Therapies^

Efficacy Parameter	FORXIGA 10 mg + insulin with/without up to 2 antidiabetic therapies	Placebo + insulin with/without up to 2 antidiabetic therapies
Intent-to-Treat Population	N=194[†]	N=193[†]
HbA1c (%)		
Baseline (mean)	8.58	8.46
Change from baseline (adjusted mean[‡])	−0.90	−0.30
Difference from placebo (adjusted mean[‡]) (95% CI)	−0.60[§] (−0.74, −0.45)	
Mean Daily Insulin Dose (IU)[††]		
Baseline (mean)	77.96	73.96
Change from baseline (adjusted mean[‡])	−1.16	5.08
Difference from placebo (95% CI)	−6.23[§] (−8.84, −3.63)	
Percent of patients with mean daily insulin dose reduction of at least 10% adjusted for baseline	19.7%**	11.0%
FPG (mmol/L)		
Baseline (mean)	9.6	9.4
Change from baseline (adjusted mean[‡])	-1.2	0.2
Difference from placebo (adjusted mean[‡]) (95% CI)	−1.4[§] (−1.9, −0.9)	
Body Weight (kg)		
Baseline (mean)	94.63	94.21
Change from baseline (adjusted mean[‡])	−1.67	0.02
Difference from placebo (adjusted mean[‡])	−1.68[§]	

Table 6: Results of 24-Week (LOCF*) Placebo-Controlled Study of FORXIGA in Combination with Insulin with or without up to 2 Oral Antidiabetic Therapies^

Efficacy Parameter	FORXIGA 10 mg + insulin with/without up to 2 antidiabetic therapies	Placebo + insulin with/without up to 2 antidiabetic therapies
(95% CI)	(−2.19, −1.18)	

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

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

‡ Least squares mean adjusted for baseline value.

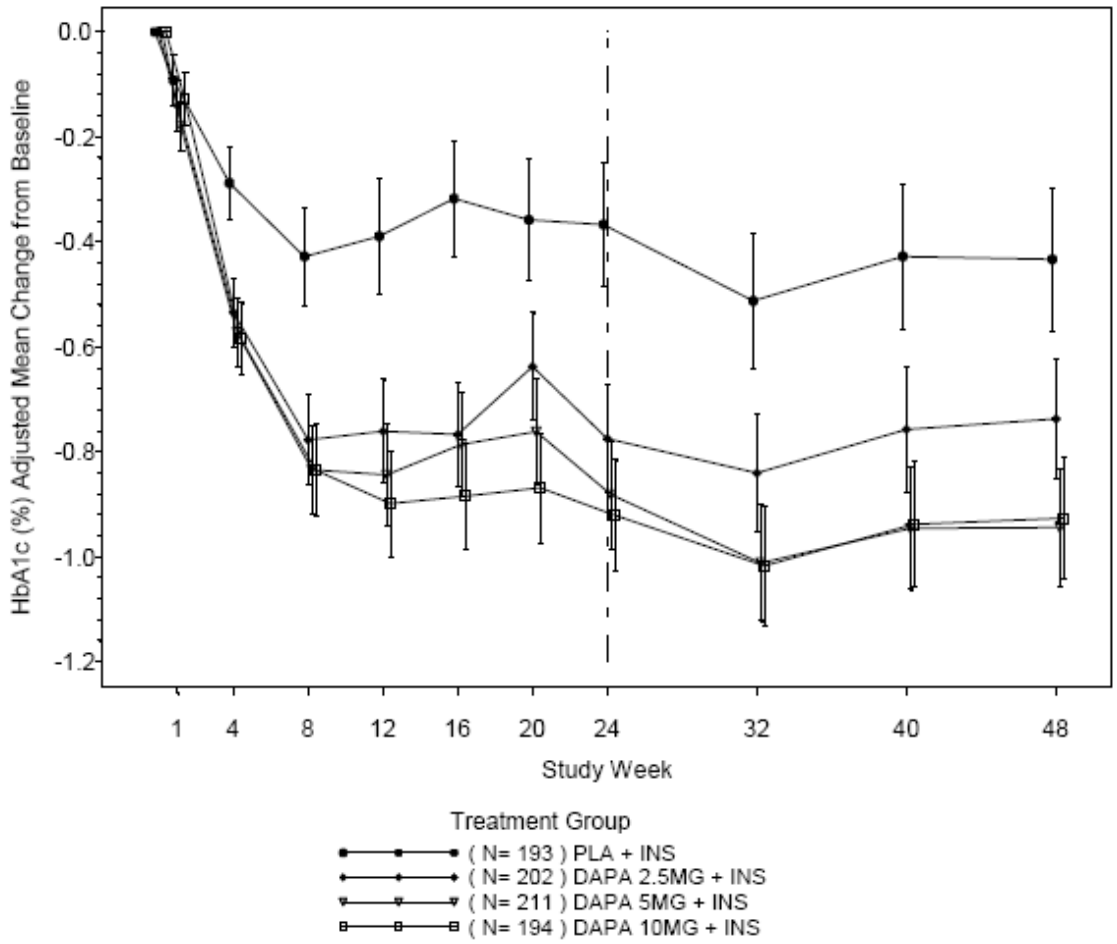
§ p-value <0.0001 versus placebo.

** p-value <0.05 versus placebo.

^ The other oral agents comprised metformin alone (40%), metformin plus sulphonylurea (5.8%) or other combinations (4.4%).

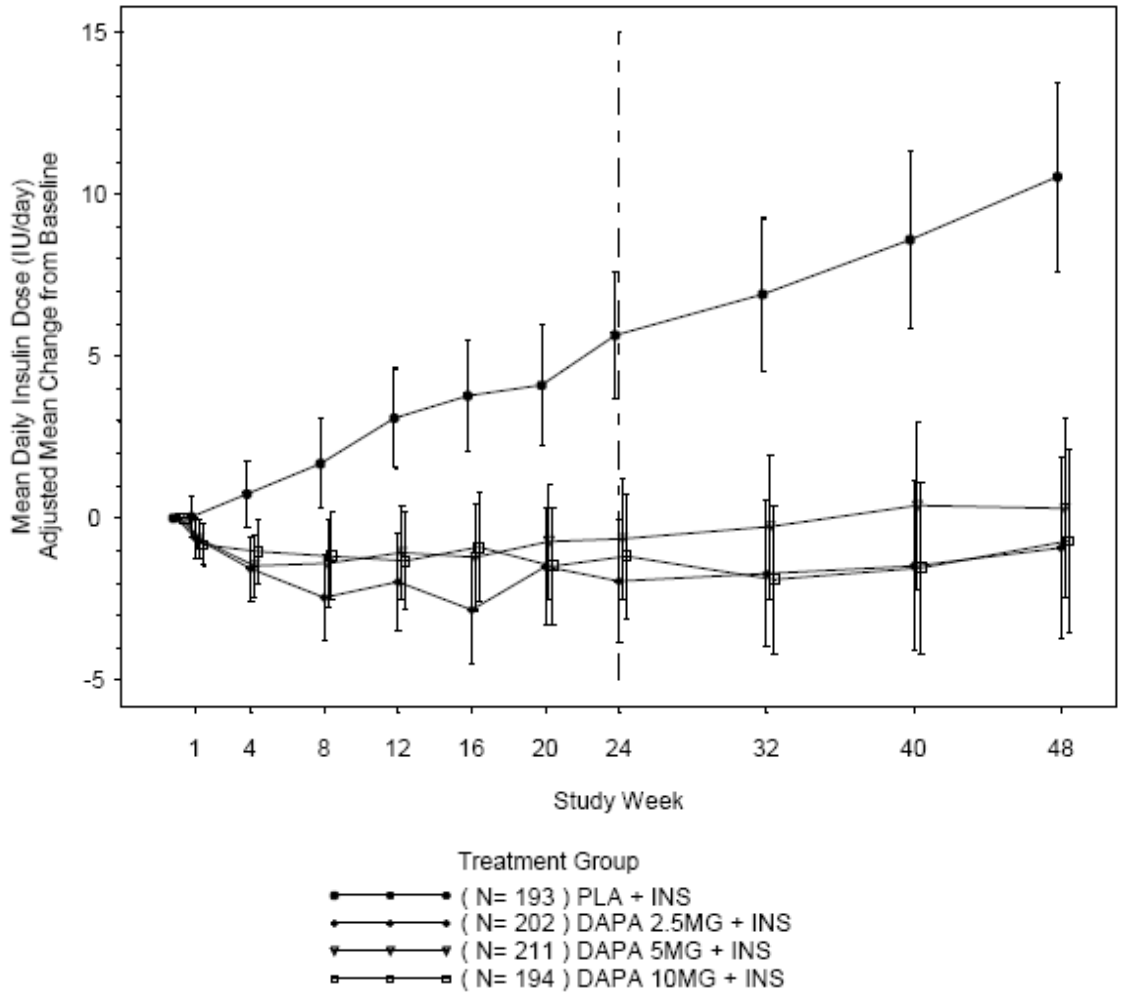
†† LOCF: last observation (after rescue) carried forward.

Figure 10: HbA1c (%) Adjusted Mean Change from Baseline Over Time Short-term and Long-term Treatment Period in a Placebo-controlled Study of FORXIGA in Combination with Insulin with or without up to 2 Oral Anti-diabetic Therapies Excluding Data After Insulin Up-titration.



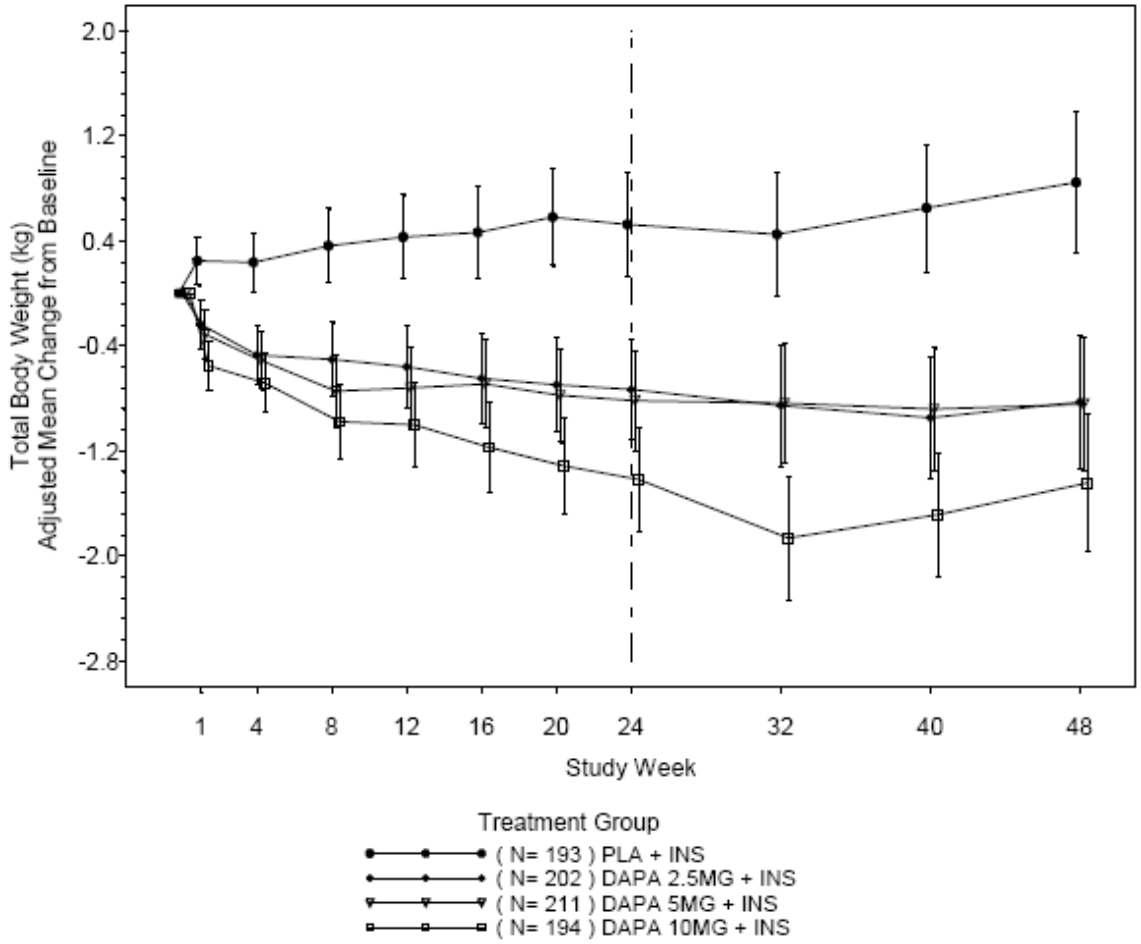
Error bars represent 95% confidence intervals for the adjusted mean change from baseline

Figure 11: Mean Daily Insulin Dose (IU/day) Adjusted Mean Change from Baseline Over Time in a Placebo-controlled Study of FORXIGA in Combination with Insulin with or without up to 2 Oral Anti-diabetic Therapies Short-term and Long-term Treatment Period Including Data After Insulin Up-titration



Error bars represent 95% confidence intervals for the adjusted mean change from baseline

Figure 12: Total Body Weight (kg) Adjusted Mean Change from Baseline Over Time in a Placebo-controlled Study of FORXIGA in Combination with Insulin with or without up to 2 Oral Anti-diabetic Therapies Short-term and Long-term Treatment Period Including Data After Insulin Up-titration



Error bars represent 95% confidence intervals for the adjusted mean change from baseline

Supportive Studies

Diabetic Patients with Moderate Renal Impairment

A study of type 2 diabetes patients with moderate renal impairment was completed to assess glycemic and safety parameters in this population. Treatment with FORXIGA was not associated with clinically relevant or statistically significant improvements in HbA1c compared with placebo in the overall study population (see also PRECAUTIONS – Use in patients with renal impairment).

Dual Energy X-ray Absorptiometry in Diabetic Patients

Due to the mechanism of action of FORXIGA a study was done to evaluate body composition and bone mineral density. FORXIGA 10 mg added on to metformin in 182 patients with type 2 diabetes over a 24 week period provided significant improvements compared with placebo plus metformin, respectively, in body weight (mean change from baseline: -2.96 kg v. -0.88 kg); waist circumference (mean change from baseline: -2.51

cm v. -0.99 cm), and body fat mass as measured by DXA (mean change from baseline -2.22 kg v. -0.74 kg) rather than lean tissue or fluid loss. FORXIGA plus metformin treatment showed a numerical decrease in visceral adipose tissue compared with placebo plus metformin treatment (change from baseline -322.6 cm^3 vs. -8.7 cm^3) in an MRI substudy. In an ongoing extension of this study to week 50, there was no important change in bone mineral density for the lumbar spine, femoral neck or total hip seen in either treatment group (mean change from baseline for all anatomical regions <0.5%, 7/89 dapagliflozin and 4/91 comparator subjects showed a decrease of 5% or more). The study will continue to week 102.

Blood Pressure

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

INDICATIONS

Monotherapy

FORXIGA is indicated as an adjunct to diet and exercise in patients with type 2 diabetes mellitus for whom metformin is otherwise indicated but was not tolerated.

Initial combination

FORXIGA is indicated for use as initial combination therapy with metformin, as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes mellitus when diet and exercise have failed to provide adequate glycemic control and there are poor prospects for response to metformin monotherapy (for example, high initial HbA1c levels).

Add-on combination

FORXIGA is indicated in patients with type 2 diabetes mellitus to improve glycemic control:

- in combination with metformin, when metformin alone with diet and exercise does not provide adequate glycemic control;
- in combination with a sulfonylurea (SU), when a SU alone with diet and exercise does not provide adequate glycemic control;
- in combination with insulin (alone or with one or both of metformin or a sulfonylurea [SU]) when the existing therapy, along with diet and exercise, does not provide adequate glycemic control.

CONTRAINDICATIONS

Known hypersensitivity to any of the ingredients.

As the efficacy of FORXIGA is dependent on renal function (see PRECAUTIONS), patients with moderately or severely impaired renal function (CrCl < 60 mL/min or eGFR < 60 mL/min/1.73 m^2).

PRECAUTIONS

FORXIGA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Use in Patients with Renal Impairment

The efficacy of FORXIGA is dependent on renal function. FORXIGA should not be used in patients with moderate renal impairment (eGFR <60 mL/min/1.73m^2 by MDRD or CrCl <60 mL/min by Cockcroft-Gault). (See DOSAGE and ADMINISTRATION, CONTRAINDICATIONS, PRECAUTIONS and ADVERSE EFFECTS.)

Monitoring of renal function is recommended as follows:
- prior to initiation of FORXIGA and at least yearly thereafter;
- prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter;
- for renal function approaching moderate renal impairment, at least 2 to 4 times per year. If renal function falls below CrCl < 60 mL/min or eGFR < 60 mL/min/1.73 m^2, treatment with FORXIGA should be discontinued (see CONTRAINDICATIONS).

FORXIGA has not been studied in patients with severe renal impairment (eGFR <30 mL/min/1.73m2 by MDRD or CrCl 30 mL/min by Cockcroft-Gault) or end stage renal disease (ESRD) and should, therefore, also not be used in this population. Based on the mechanism of action, FORXIGA was not anticipated to be effective in these populations.

Patients with mild renal impairment (eGFR ≥60 to <90 mL/min/1.73m^2)

The clinical program included 51% (3166/6228) of patients with mild renal impairment. 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 hemoglobin A1c (HbA1c) and the placebo-corrected mean HbA1c change at 24 weeks was -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.

Patients with moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73m^2)

The efficacy of FORXIGA is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment. Therefore, FORXIGA should not be used in patients with moderate to severe renal impairment (eGFR <60 mL/min/1.73m^2 by MDRD or CrCl <60 mL/min by Cockcroft-Gault). (See DOSING and ADMINISTRATION - Renal Impairment).

The clinical program included 11% (684/6228) of patients with moderate renal impairment.

Efficacy in patients with moderate renal impairment was assessed in a pooled analysis across 9 clinical studies (366 patients, 87% with eGFR ≥45 to <60 mL/min/1.73m^2). The mean change from baseline in HbA1c and the placebo-corrected mean HbA1c reduction at 24 weeks was -0.87% and -0.39%, respectively, for FORXIGA 10 mg (n=85).

The efficacy of FORXIGA was also separately assessed in a dedicated study of diabetic patients with moderate renal impairment (252 patients with mean eGFR 44 mL/min/1.73m^2). The mean change from baseline in HbA1c and the placebo-corrected mean HbA1c change at 24 weeks was -0.44% and -0.11%, respectively, for FORXIGA 10 mg (n=82). An additional analysis by eGFR subgroups (eGFR ≥45 and eGFR <45 mL/min/1.73m^2) in this study was conducted. In patients with baseline eGFR ≥45 to <60 mL/min/1.73m^2, the mean change from baseline in HbA1c and the placebo-corrected mean HbA1c change at 24 weeks was -0.44% and -0.33%, respectively, for FORXIGA 10 mg (n=32). In patients with eGFR ≥30 to <45 mL/min/1.73m^2 in this study, the mean change from baseline in HbA1c and the placebo-corrected mean HbA1c change at 24 weeks was -0.45% and 0.07%, respectively, for FORXIGA 10 mg (n=45). These results are consistent with the mechanism of action of FORXIGA which is dependent on renal function (see PHARMACOLOGY).

Safety in patients with moderate renal impairment was assessed in a pooled analysis of 12 clinical studies (384 patients, 88% with eGFR ≥45 to < 60 mL/min/1.73m^2); this pool does not include the dedicated study of diabetic patients with moderate renal impairment. At Week 24, safety was similar to that seen in the overall clinical program except for a higher proportion of patients reporting at least one event related to renal impairment or failure (7.9% FORXIGA 10 mg vs. 5.6% placebo). Of these events, increased serum creatinine was the most frequently reported (6.7% FORXIGA 10 mg vs. 2.8% placebo). Increases in mean parathyroid hormone (PTH) and serum phosphorus observed with FORXIGA in the overall clinical program were also seen in the pooled analysis. No imbalance in bone fractures was observed in this analysis. In the short-term plus long-term safety pool up to 102 weeks, the safety profile remained similar.

In the dedicated moderate renal impairment study at Week 52, FORXIGA was associated with changes from baseline in mean eGFR and eCrCl (eGFR: FORXIGA 10 mg -4.46 mL/min/1.73m^2 and placebo -2.58 mL/min/1.73m^2 eCrCl: FORXIGA 10 mg -7.27 mL/min and placebo -2.56 mL/min). With FORXIGA 10 mg, these reductions were evident at week 1 and remained stable through to week 52 while placebo treated patients had a slow continuous decline through to week 52.

At week 52, greater increases in mean PTH and serum phosphorus were observed in this study, where baseline values of these analytes were higher. A higher frequency of bone fractures was observed in groups treated with FORXIGA 10 mg (8.2%) compared with placebo (0%). Two of these seven fractures occurred in patients with eGFR ≥45 to <60 mL/min/1.73m^2.

Efficacy was similarly reduced for dapagliflozin 5 mg while the safety profile was comparable to that of FORXIGA 10 mg in the eGFR ≥45 to <60 mL/min/1.73m^2 cohort of patients.

Use in patients with severe hepatic impairment

There is limited experience in clinical trials in patients with hepatic impairment. Dapagliflozin exposure is increased in patients with severe hepatic impairment. FORXIGA should not be used in patients with severe hepatic impairment (see DOSAGE AND ADMINISTRATION and PHARMACOLOGY).

Use in Patients at Risk for Volume depletion

The diuretic effect of FORXIGA is a potential concern for volume depleted patients. Dapagliflozin is not recommended for use in patients receiving loop diuretics or who are volume depleted.

When considering initiating dapagliflozin, there may be patients for whom the additional diuretic effect of dapagliflozin is a potential concern either due to acute illness (such as gastrointestinal illness) or a history of hypotension or dehydration with diuretic therapy for patients who may become volume depleted. Initiation of therapy with dapagliflozin is therefore not recommended in these patients.

For patients receiving dapagliflozin, in case of intercurrent conditions that may lead to volume depletion, such as gastrointestinal illness, heat stress or severe infections, careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended. Temporary interruption of FORXIGA is recommended for patients who develop volume depletion until the depletion is corrected (see ADVERSE EFFECTS).

Urinary Tract Infections

Urinary tract infections were more frequently reported for FORXIGA 10 mg compared to control in a placebo-pooled analysis up to 24 weeks (4.3% vs. 3.7%, respectively). Pyelonephritis was uncommon and presented in similar frequencies for FORXIGA and control groups (0 patients FORXIGA 10 mg and 1 patient treated with placebo). Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of FORXIGA should be considered when treating pyelonephritis or urosepsis (see ADVERSE EFFECTS). Discontinuation of FORXIGA may be considered in cases of recurrent urinary tract infections.

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 EFFECTS).

Effects on Fertility

In a study of fertility in rats, no effects on mating, fertility, or early embryonic development were seen when males received oral doses up to 210 mg/kg/day or when females received oral doses up to 75 mg/kg/day (yielding plasma AUC values at least 1000 times the clinical exposure at the maximum recommended human dose [MRHD] of 10 mg/day). However, at 210 mg/kg/day, a dose associated with profound toxicity (including mortality), seminal vesicle and epididymal weights were reduced; sperm motility and sperm counts were reduced; and there were increased numbers of

morphologically abnormal sperm. No adverse effects on sperm or male reproductive organs were seen at 75 mg/kg/day (700 times the clinical exposure at the MRHD).

Use in Pregnancy – Category D

There are no data from the use of dapagliflozin in pregnant women. Studies in rats have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy (see PRECAUTIONS). Therefore, FORXIGA must not be used during the second and third trimesters of pregnancy. When pregnancy is detected, treatment with FORXIGA should be discontinued.

In conventional studies of embryofoetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the period of organogenesis in humans. An increased incidence of embryofoetal lethality, decreased foetal weight and an increased incidence of foetal visceral and skeletal anomalies were seen in rats at maternotoxic doses (oral doses greater than or equal to 150 mg/kg/day). The no observed effect level for embryofoetal effects in rats was an oral dose of 75 mg/kg/day (1530 times the exposure in patients at the maximum recommended human dose [MRHD]). No developmental toxicities were observed in rabbits at oral doses up to 180 mg/kg/day (1265 times the exposure in patients at the MRHD).

Use in Lactation

FORXIGA must not be used by breastfeeding women. It is not known whether dapagliflozin or its metabolites are excreted in human milk. Studies in rats have shown excretion of dapagliflozin in milk. Direct and indirect exposure of dapagliflozin to weanling juvenile rats and during late pregnancy are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny.The long-term functional consequences of these effects are unknown. These periods of exposure coincide with a critical window of renal maturation in rats. As functional maturation of the kidneys in humans continues in the first 2 years of life, dapagliflozin-associated dilated renal pelvis and tubules noted in juvenile rats could constitute potential risk for human renal maturation during the first 2 years of life. Additionally, the negative effects on body weight gain associated with lactational exposure in weanling juvenile rats suggest that FORXIGA must be avoided during the first 2 years of life.

Paediatric Use

Safety and effectiveness of FORXIGA in paediatric patients have not been established. Delayed growth and metabolic acidosis in rats were observed in both sexes at higher doses (greater than or equal to 15 mg/kg/day). The developmental age of animals in this study approximately correlates to 2 to 16 years in humans.

Use in the Elderly

Elderly patients are more likely to have impaired renal function, and/or to be treated with anti hypertensive medicinal products that may cause changes in renal function such as angiotensin converting enzyme inhibitors (ACE-I) and angiotensin II type 1 receptor blockers (ARB). The same recommendations for renal function apply to elderly patients as to all patients (see PRECAUTIONS, Use in Patients with Renal Impairment and DOSAGE AND ADMINISTRATION).

In subjects ≥ 65 years of age, a higher proportion of subjects treated with dapagliflozin had events adverse reactions related to renal impairment or failure compared with

placebo. The most commonly reported adverse reactions related to renal function was increased blood serum creatinine increases, the majority of which were transient and reversible (see section ADVERSE REACTIONS).

Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics. In subjects ≥ 65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse reactions related to volume depletion (see section ADVERSE REACTIONS).

Therapeutic experience in patients 75 years and older is limited. Initiation of dapagliflozin therapy in this population is not recommended (see sections ADVERSE REACTIONS and PHARMACOLOGY, Pharmacokinetics).

Combinations not studied

Dapagliflozin has not been studied in combination with dipeptidyl peptidase 4 (DPP-4) inhibitors or glucagon like peptide 1 (GLP-1) analogues.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with FORXIGA or any other antidiabetic drug. In a prospective meta-analysis of 14 clinical studies, FORXIGA use was not associated with an increased risk for adverse cardiovascular events (see section ADVERSE EFFECTS).

Carcinogenicity

Dapagliflozin did not induce tumours in two-year carcinogenicity studies in mice or rats at oral doses up to 40 mg/kg/day and 10 mg/kg/day respectively. These doses correspond to AUC exposure levels at least 78 times the human AUC at the MRHD of 10 mg/day.

Use in patients treated with pioglitazone

While a causal relationship between dapagliflozin and bladder cancer is unlikely (see Adverse Effects), as a precautionary measure, dapagliflozin is not recommended for use in patients concomitantly treated with pioglitazone. Available epidemiological data for pioglitazone suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone.

Genotoxicity

Dapagliflozin was positive in an *in-vitro* clastogenicity assay in the presence of metabolic activation. However, dapagliflozin was negative in the Ames mutagenicity assay andand in a series of *in-vivo* clastogenicity studies evaluating micronuclei or DNA repair in rats at exposure multiples at least 2100 times the human exposure at the MRHD. The weight of evidence from these studies, along with the absence of tumour findings in the rat and mouse carcinogenicity studies, support that dapagliflozin is not genotoxic.

Interactions with Other Medicines

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 neither inhibited CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, nor induced CYP1A2, 2B6 or 3A4. Therefore, dapagliflozin is not expected to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes and drugs which inhibit or induce these enzymes are not expected to alter the metabolic clearance of dapagliflozin. Dapagliflozin is a weak substrate of the P-glycoprotein (P-gp) active transporter and dapagliflozin 3-O-glucuronide is a substrate for the OAT3 active transporter. Dapagliflozin or dapagliflozin 3-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.

Effect of Other Drugs on Dapagliflozin

In studies conducted in healthy subjects, the pharmacokinetics of dapagliflozin were not altered by metformin, pioglitazone (a CYP2C8 [major] and CYP3A4 [minor] substrate), sitagliptin (an hOAT-3 substrate and P-glycoprotein substrate), glimepiride, hydrochlorothiazide, bumetanide, valsartan, or simvastatin A 22% decrease in dapagliflozin systemic exposure following coadministration with rifampacin and a 51% increase in dapagliflozin systemic exposure following coadministration with mefenamic acid were considered not to be large enough to warrant a dose adjustment.

Mefenamic Acid: Coadministration of a single dose of dapagliflozin (10 mg) and mefenamic acid, an inhibitor of UGT1A9, dosed to steady-state (250 mg every 6 hours) resulted in an increase in dapagliflozin Cmax and AUC by 13% and 51%, respectively. The mean amount of glucose excreted in the urine over 24 hours following administration of dapagliflozin alone was not markedly affected by mefenamic acid coadministration. No dose adjustment of dapagliflozin is recommended when dapagliflozin is coadministered with mefenamic acid.

Metformin: Coadministration of a single dose of dapagliflozin (20 mg) and metformin (1000 mg), an hOCT-1 and hOCT-2 substrate, did not alter the pharmacokinetics of dapagliflozin. Therefore, meaningful interactions of FORXIGA with other hOCT-1 and hOCT-2 substrates would not be expected.

Pioglitazone: Coadministration of a single dose of dapagliflozin (50 mg) and pioglitazone (45 mg), a CYP2C8 (major) and CYP3A4 (minor) substrate, did not alter the pharmacokinetics of dapagliflozin. Therefore, meaningful interactions of FORXIGA with other CYP2C8 substrates would not be expected.

Sitagliptin: Coadministration of a single dose of dapagliflozin (20 mg) and sitagliptin (100 mg), an hOAT-3 substrate, did not alter the pharmacokinetics of dapagliflozin. Therefore, meaningful interactions of FORXIGA with other hOAT-3 substrates would not be expected.

Glimepiride: Coadministration of a single dose of dapagliflozin (20 mg) and glimepiride (4 mg), a CYP2C9 substrate, did not alter the pharmacokinetics of dapagliflozin. Therefore, meaningful interactions of FORXIGA with other CYP2C9 substrates would not be expected.

Hydrochlorothiazide: Coadministration of a single dose of dapagliflozin (50 mg) and hydrochlorothiazide (25 mg) did not alter the pharmacokinetics of dapagliflozin.

Bumetanide: Coadministration of multiple once-daily doses of dapagliflozin (10 mg) and multiple once-daily doses of bumetanide (1 mg) did not alter the pharmacokinetics of dapagliflozin. Coadministration of dapagliflozin and bumetanide did not meaningfully change the pharmacodynamic effect of dapagliflozin to increase urinary glucose excretion in healthy subjects.

Valsartan: Coadministration of a single dose of dapagliflozin (20 mg) and valsartan (320 mg) did not alter the pharmacokinetics of dapagliflozin.

Simvastatin: Coadministration of a single dose of dapagliflozin (20 mg) and simvastatin (40 mg), a CYP3A4 substrate, did not alter the pharmacokinetics of dapagliflozin. Therefore, meaningful interactions of FORXIGA with other CYP3A4 substrates would not be expected.

Rifampacin: Coadministration of a single dose of dapagliflozin (10 mg) and rifampacin (rifampicin), an inducer of various active transporters and drug-metabolizing enzymes, dosed to steady-state [600 mg/day] resulted in a decrease in dapagliflozin Cmax and AUC by 7 and 22%, respectively. The mean amount of glucose excreted in the urine over 24 h following administration of dapagliflozin alone (51 g) was not markedly affected by rifampacin coadministration (45 g). No dose adjustment of dapagliflozin is recommended when dapagliflozin is coadministered with rifampacin.

Effect of Dapagliflozin on Other Drugs

In studies conducted in healthy subjects, as described below, dapagliflozin did not alter the pharmacokinetics of metformin, pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, simvastatin, digoxin or warfarin.

Metformin: Coadministration of a single dose of dapagliflozin (20 mg) and metformin (1000 mg), an hOCT-1 and hOCT-2 substrate, did not alter the pharmacokinetics of metformin. Therefore, FORXIGA is not an inhibitor of hOCT-1 and hOCT-2-mediated transport.

Pioglitazone: Coadministration of a single dose of dapagliflozin (50 mg) and pioglitazone (45 mg), a CYP2C8 (major) and CYP3A4 (minor) substrate, did not alter the pharmacokinetics of pioglitazone. Therefore, FORXIGA does not meaningfully inhibit CYP2C8-mediated metabolism.

Sitagliptin: Coadministration of a single dose of dapagliflozin (20 mg) and sitagliptin (100 mg), an hOAT-3 substrate, did not alter the pharmacokinetics of sitagliptin. Therefore, FORXIGA is not an inhibitor of hOAT-3 transport pathway.

Glimepiride: Coadministration of a single dose of dapagliflozin (20 mg) and glimepiride (4 mg), a CYP2C9 substrate, did not alter the pharmacokinetics of glimepiride. Therefore, FORXIGA is not an inhibitor of CYP2C9 mediated metabolism.

Hydrochlorothiazide: Coadministration of a single dose of dapagliflozin (50 mg) and hydrochlorothiazide (25 mg) did not alter the pharmacokinetics of hydrochlorothiazide.

Bumetanide: Coadministration of a multiple once-daily doses of dapagliflozin (10 mg) and multiple once-daily doses of bumetanide (1 mg) increased both Cmax and AUC bumetanide values by 13%. Coadministration of dapagliflozin did not meaningfully alter

the steady-state pharmacodynamic responses (urinary sodium excretion, urine volume) to bumetanide in healthy subjects.

Valsartan: Coadministration of a single dose of dapagliflozin (20 mg) and valsartan (320 mg) did not alter the pharmacokinetics of valsartan.

Simvastatin: Coadministration of a single dose of dapagliflozin (20 mg) and simvastatin (40 mg), a CYP3A4 substrate, did not affect the Cmax of simvastatin but increased the AUC of by 20% which was not considered to be clinically relevant. Therefore, FORXIGA does not meaningfully inhibit CYP3A4-mediated metabolism.

Digoxin: Coadministration of dapagliflozin (10 mg once daily following a 20 mg loading dose) and a single dose of digoxin (0.25 mg), a P-glycoprotein substrate, did not affect the pharmacokinetics of digoxin. Therefore, dapagliflozin does not meaningfully inhibit or induce P-gp-mediated transport.

Warfarin: Coadministration of dapagliflozin (10 mg once daily following a 20 mg loading dose) and a single dose of warfarin (25 mg) did not affect the pharmacokinetics of S-warfarin, a CYP2C19 substrate. Therefore, dapagliflozin does not meaningfully inhibit or induce CYP2C19-mediated metabolism. Dapagliflozin also did not affect the pharmacokinetics of R-warfarin. Additionally, dapagliflozin did not affect the anticoagulant activity of warfarin as measured by the prothrombin time (International Normalized Ratio; [INR]).

Other Interactions

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

Effects on Laboratory Tests

Haematocrit

In the placebo-pooled analysis, increases from baseline in mean haematocrit 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. At week 24, the mean changes from baseline in haematocrit were 2.15% in the FORXIGA 10 mg group vs. -0.40% in the placebo group. At week 50, the mean changes were 2.51% vs. -0.29%, respectively. By week 24, haematocrit values > 55% were reported in 1.3% of FORXIGA 10 mg treated patients vs. 0.3% of placebo 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).

Serum Inorganic Phosphorus

Increases from baseline in mean serum phosphorus levels were reported at week 24 in FORXIGA 10 mg treated patients compared with placebo (mean increases of 54.9 µmol/L vs. 9.7 µmol/L, respectively). Similar results were seen at week 50. Higher proportions of patients with marked laboratory abnormalities of hyperphosphataemia (≥ 1.81 mmol/L if age 17 - 65 or ≥ 1.65 mmol/L if ≥ age 66) were reported in FORXIGA 10 mg group vs. placebo at week 24 (1.7% vs. 0.7%, respectively) and during the short-term plus long-term phase (2.6% vs. 1.5%, respectively). The clinical relevance of these findings is unknown.

Lipids

Small changes from baseline in mean lipid values were reported at week 24 in FORXIGA 10 mg treated patients compared with placebo. Mean percent change from baseline at week 24 for FORXIGA 10 mg vs. placebo, respectively was as follows: total cholesterol 1.4% vs.-0.4%; HDL cholesterol 5.5% vs.3.8%; LDL cholesterol 2.7% vs. -1.9%; triglycerides -5.4% vs. 0.7%. Mean percent change from baseline at week 50 for FORXIGA 10 mg vs. placebo, respectively was as follows: total cholesterol 1.5% vs.-0.7%; HDL cholesterol 6.5% vs.2.5%; LDL cholesterol 3.5% vs. -0.7%; triglycerides -3.9% vs. 0.5%. The ratio between LDL cholesterol and HDL cholesterol decreased for all treatment groups at week 24.

Liver Function Tests

There were no increases in mean ALT or AST levels, and there was no imbalance across treatment groups in liver enzyme elevations. In the placebo-pooled analysis, ALT >3 x ULN was reported in 0.8% on FORXIGA 10 mg and 1.1% on placebo over 24 weeks. In the overall clinical program, ALT or AST >3 x ULN and bilirubin >2 x ULN was reported in 5 patients (0.1%) on FORXIGA and 3 patient (0.2%) on comparator. One patient receiving FORXIGA experienced a liver adverse event with diagnoses of drug induced hepatitis and autoimmune hepatitis.

Effects on Ability to Drive and to Use Machines

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

ADVERSE EFFECTS

A total of 6228 patients with type 2 diabetes were randomized, including 4287 patients treated with FORXIGA, in 14 double-blind, controlled, clinical safety and efficacy studies conducted to evaluate the effects of FORXIGA on glycemic control. FORXIGA 10 mg was evaluated in 12 of these studies. In a pre-specified pooled analysis of 12 placebo controlled studies including the monotherapy studies, add-on studies, and the initial combination with metformin studies, 1193 patients were treated with FORXIGA 10 mg and 1393 were treated with placebo (both as monotherapy or in combination with other antidiabetic therapies). The overall incidence of adverse events (short term treatment) in patients treated with FORXIGA 10 mg was 61.5% compared to 56.9% for the placebo group. The incidence of discontinuation of therapy due to adverse events in patients who received FORXIGA 10 mg was 3.2% compared to 2.5% for the placebo group. The most commonly reported events leading to discontinuation in patients treated with FORXIGA 10 mg were increased blood creatinine (0.4%), urinary tract infections (0.3%), nausea (0.2%), dizziness (0.2%), and rash (0.2%).

The adverse reactions reported (regardless of investigator assessment of causality) in ≥2% of patients treated with FORXIGA 10 mg and ≥1% more frequently than patients treated with placebo are shown in Table 8.

Table 7 Adverse reactions (Regardless of Investigator Assessment of Causality) in Placebo-Controlled Studies* Reported in ≥2% of Patients Treated with FORXIGA 10 mg and ≥1% More Frequently than in Patients Treated with Placebo†

System organ class Preferred term	% of patients	
	FORXIGA 10mg N=1193	PLACEBO N=1393
Infections and infestations		
Genital Infection§	4.8	0.9
Musculoskeletal and Connective Tissue Disorders		
Back pain	4.2	3.2
Renal and Urinary disorders		
Polyuria¶	3.8	1.7
Dysuria	2.1	0.7
Metabolism and nutrition disorders		
Hypoglycaemia‡	10.2	7.0
Dyslipidemia	2.5	1.5

*The 12 placebo-controlled studies included 4 monotherapy, and 2 initial combination with metformin, 6 add-on studies. Table shows up to 24-week (short-term) data regardless of glycemic rescue.

†Adverse reactions occurring in ≥2% of patients and ≥1% more in patients treated with FORXIGA than control.

§Genital infection includes the preferred terms, listed in order of frequency reported: vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, and vulval abscess.

¶Polyuria includes the preferred terms, listed in order of frequency reported: pollakiuria, polyuria, urine output increased.

‡Adverse reactions of major hypoglycemia (when excluding rescue) (an episode in which the patient requires assistance or treatment and, if inadequately treated, may be life threatening) were 0.1% for FORXIGA 10 mg versus 0.1% for placebo. Adverse reactions of hypoglycemia were primarily from add-on to insulin and add-on to sulfonylureas trials (see Hypoglycemia below).

Additional adverse reactions in ≥5% of patients treated with FORXIGA 10 mg, ≥1% more than patients in placebo/comparator, and reported in at least three more patients treated with FORXIGA 10 mg and regardless of relationship to FORXIGA reported by investigator, are described below by treatment regimen.

- In the add-on to metformin studies: headache (5.3% FORXIGA 10mg and 3.1% placebo).

In a dedicated study of patients with moderate renal impairment, a higher frequency of bone fractures was observed in groups treated with FORXIGA 10 mg (8.2%) compared with placebo (0%). Two of these seven fractures occurred in patients with eGFR ≥ 45 to <60 mL/min/1.73m^2. Greater increases in mean PTH and serum phosphorus were observed in this study where baseline values were higher (see PRECAUTIONS).

Volume depletion

Events related to volume depletion (including reports of dehydration, hypovolemia or hypotension) were reported in 0.8% and 0.4% of patients who received FORXIGA 10 mg and placebo, respectively, in the short-term, placebo-pooled analysis. Serious events occurred in ≤0.2% of patients in the 14 clinical studies and were balanced between FORXIGA 10 mg and comparator (see section PRECAUTIONS).

Genital Infections

Events of genital infections were reported in 4.8% and 0.9% of patients who received FORXIGA 10 mg and placebo, respectively, in the short-term, placebo-pooled analysis. The events of genital infections reported in patients treated with FORXIGA 10 mg were all mild to moderate. Most events of genital infection responded to an initial course of standard treatment and rarely resulted in discontinuation from the study (0.2% FORXIGA 10 mg vs. 0% in placebo). Infections were more frequently reported in females (6.9% FORXIGA 10 mg vs. 1.5% placebo) than in males (2.7% FORXIGA 10 mg vs. 0.3% placebo). The most frequently reported genital infections were vulvovaginal mycotic infections (3.3% FORXIGA 10 mg vs 0.7% placebo) and vaginal infection (1.7% FORXIGA 10 mg vs 0.1% placebo) in females, and balanitis (1.2% FORXIGA 10 mg vs. 0.1% placebo) and fungal genital infection (0.8% FORXIGA 10 mg vs. 0.1% placebo) in males.

In the short-term plus long-term placebo-pooled analysis (mean duration of treatment was 453.7 days for FORXIGA 10 mg and 409.3 days for placebo); the proportions of patients with events of genital infections were 8.2% (63/768) in FORXIGA 10 mg and 1.3% (9/694) in placebo. Of the 63 patients treated with FORXIGA 10 mg who experienced an infection, 47 (74.6%) had only one and 10 (15.8%) had 3 or more. Of the 9 patients treated with placebo who experienced an infection, 7 (77.8%) had only one and none had 3 or more infections.

In the short-term, placebo-pooled analysis, patients who had a history of recurrent genital infection, were more likely to have an event of genital infection (25.0% of patients with history of infection treated with FORXIGA 10 mg and 10.0% of patients with history of infection on placebo) during the study than those without (5.0% on FORXIGA 10 mg and 0.8% on placebo).

Urinary Tract Infections

Events of urinary tract infections were reported in 4.3% and 3.7% of patients who received FORXIGA 10 mg and placebo, respectively, in the short term, placebo-pooled analysis. All events of urinary tract infections reported in patients treated with FORXIGA

10 mg were mild to moderate. Most patients responded to an initial course of standard treatment, and urinary tract infections rarely caused discontinuation from the study (0.3% FORXIGA 10 mg vs. 0.1% placebo). Infections were more frequently reported in females (7.7% FORXIGA 10 mg vs. 6.6% placebo) than in males (0.8% FORXIGA 10 mg vs. 1% placebo) (see section PRECAUTIONS).

In the short-term plus long-term placebo-pooled analysis (mean duration of treatment was 453.7 days for FORXIGA 10 mg and 409.3 days for placebo); the proportions of patients with events of urinary tract infections were 7.7% (59/768) in FORXIGA 10 mg and 6.3% (44/694) placebo. Of the 59 patients treated with FORXIGA 10 mg who experienced an infection, 44 (74.6%) had only one and 3 (5.1%) had 3 or more. Of the 44 patients treated with placebo who experienced an infection, 38 (86.4%) had only one and 3 (6.8%) had 3 or more infections.

In the short-term pool, patients who had a history of recurrent urinary tract infection, were more likely to have an event of urinary tract infection (17.6% of patients with history of infection treated with FORXIGA 10 mg and 17.1% of patients with history of infection on placebo) during the study than those without (3.7% on FORXIGA 10 mg and 3.4% on placebo).

Hypoglycemia

The frequency of hypoglycemia depended on the type of background therapy used in each study. Studies with add-on sulfonylurea and add-on insulin therapies had higher rates of hypoglycemia (see section PRECAUTIONS).

In studies of FORXIGA used in monotherapy, add-on to metformin, and initial combination with metformin up to 24 weeks, there were no major episodes of hypoglycemia with FORXIGA and the frequency of minor episodes of hypoglycemia was similar (<4%) between treatment groups, including placebo.

In an add-on to glimepiride study up to 24 weeks, no episode of major hypoglycemia was reported. Minor episodes of hypoglycemia were reported in 10 (6.6%) patients in the FORXIGA 10 mg plus glimepiride group and 3 (2.1%) patients in the placebo plus glimepiride group.

In an active glipizide controlled add-on to metformin study a significantly lower proportion of patients on FORXIGA (3.5%) experienced at least one event of hypoglycemia over 52 weeks of treatment, compared to glipizide (40.8%).

In an add-on to insulin study up to 24 weeks, episodes of major hypoglycemia were reported in 1 (0.5%) and 1 (0.5%) patient in FORXIGA 10 mg plus insulin and placebo plus insulin groups, respectively. Minor episodes were reported in 79 (40.3%) patients in the FORXIGA 10 mg plus insulin group and in 67 (34%) patients in placebo plus insulin group. Patients in this study could also be treated with a maximum of two oral anti-diabetes medications (OADs) including metformin.

Malignancies

During clinical trials, the overall proportion of subjects with malignant or unspecified tumours was similar between those treated with FORXIGA (1.47%) and placebo/comparator (1.35%), and there was no carcinogenicity or mutagenicity signal in animal data (see section 5.3). When considering the cases of tumours occurring in the different organ systems, the relative risk associated with FORXIGA was above 1 for some tumours (bladder, prostate, breast) and below 1 for others (e.g. blood and lymphatic, ovary, renal tract), not resulting in an overall increased tumour risk associated with FORXIGA. The increased/decreased risk was not statistically significant in any of the organ systems. Considering the lack of tumour findings in non-clinical studies as well as the short latency between first drug exposure and tumour diagnosis, a causal relationship is considered unlikely. Since the numerical imbalance of breast, bladder and prostate tumours must be considered with caution, it will be further investigated in post-authorisation studies.

Cardiovascular Safety

A meta-analysis of cardiovascular events in the clinical program was performed. In the clinical program, 36.6% of subjects had a history of cardiovascular disease (excluding hypertension) at baseline and 70.0% had hypertension. Cardiovascular events were adjudicated by an independent adjudication committee. The primary endpoint was the time to first event of the following outcomes: cardiovascular death, stroke, myocardial infarction, and hospitalization for unstable angina. Primary events occurred at a rate of 1.64% per patient-year in patients treated with FORXIGA and 1.99% in comparator-treatment patients, per patient-year. The hazard ratio comparing FORXIGA to comparator was 0.82 (95% confidence interval: 0.58, 1.15), indicating that in this analysis, FORXIGA is not associated with an increase in cardiovascular risk in patients with type 2 diabetes mellitus. Cardiovascular death, MI and stroke were observed with a hazard ratio of 0.79 (95% CI: 0.54, 1.17).

Vital Signs

A decrease in blood pressure (mean seated systolic blood pressure change from baseline at week 24 of 4.4 mmHg and mean seated diastolic blood pressure change of 2.1 mmHg for FORXIGA 10 mg vs. 0.9 mmHg systolic and 0.5 mmHg diastolic blood pressure change for placebo group) was observed with FORXIGA without any increased incidence of orthostatic hypotension. No other clinically meaningful changes in vital signs have been observed in patients with FORXIGA.

DOSAGE AND ADMINISTRATION

Recommended dosage

The recommended dose of FORXIGA is 10 mg taken once daily at any time of the day regardless of meals.

Monotherapy and Add-On Combination Therapy

The recommended dose of FORXIGA is 10 mg once daily as monotherapy or as add-on to combination therapy with metformin, a sulfonylurea, or insulin (alone or with one or both of metformin or a sulfonylurea [SU]).

Initial Combination Therapy

The recommended starting doses of FORXIGA and metformin when used as initial combination therapy are 10 mg FORXIGA plus 500 mg metformin once daily. Patients with inadequate glycemic control on this starting dose should have their metformin dose increased according to approved metformin Product Information.

Renal impairment

No dosage adjustment for FORXIGA is recommended in patients with mild renal impairment.

FORXIGA should not be used in patients with moderate to severe renal impairment (eGFR <60 mL/min/1.73 m^2 by MDRD or CrCl <60 mL/min by Cockcroft-Gault) (see PRECAUTIONS AND CONTRAINDICATIONS).

Hepatic Impairment

No dosage adjustment for FORXIGA is necessary for patients with mild or moderate hepatic impairment. FORXIGA should not be used in patients with severe hepatic impairment (see PRECAUTIONS).

Paediatric and adolescent

Safety and effectiveness of FORXIGA in paediatric and adolescent patients have not been established.

Elderly

In general, no dosage adjustment is recommended based on age. Renal function and risk of volume depletion should be taken into account (see PRECAUTIONS and PHARMACOLOGY). Due to the limited therapeutic experience in patients 75 years and older, initiation of dapagliflozin therapy is not recommended in this patient group.

OVERDOSAGE

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

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

PRESENTATION AND STORAGE CONDITIONS

FORXIGA (dapagliflozin) 10 mg tablets are yellow, biconvex, diamond, film coated tablets in aluminium/aluminium blisters in pack sizes of 7 and 28 tablets.

The tablets should be stored below 30°C.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (Schedule 4).

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

22 October 2012