FORXIGA®

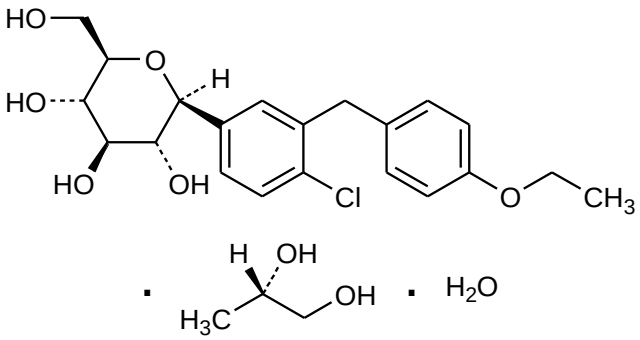
dapagliflozin propanediol monohydrate

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 chemical structure of dapagliflozin propanediol monohydrate is:



CAS Number: 960404-48-2

Molecular formula: $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$

Molecular weight: 502.98

DESCRIPTION

Dapagliflozin drug substance is a white to off-white powder, is non-hygroscopic, crystalline. Dapagliflozin is non-ionizable; thus, its aqueous solubility and partition coefficient are not affected by changes in pH. Dapagliflozin is a Biopharmaceutical Classification System (BCS) Class III drug.

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 glycaemic 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. 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 hypoglycaemia. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. 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. 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. Evidence of sustained glucose excretion was seen in patients with type 2 diabetes mellitus given dapagliflozin 10 mg/day for up to 2 years.

This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume. 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.

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 (C_{max}) were usually attained within 2 hours after administration in the fasted state. The C_{max} 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 C_{max} by up to 50% and prolonged T_{max} by approximately 1 hour, but did not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful.

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 a 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 ($t_{1/2}$) for dapagliflozin was 12.9 hours following a single oral dose of FORXIGA 10 mg to healthy subjects.

Special Populations

No dosage 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

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. FORXIGA should not be used in patients with moderate or severe renal impairment (CrCl persistently <60 mL/min or eGFR persistently <60 mL/min/1.73m^2), see CONTRAINDICATIONS and PRECAUTIONS.

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 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 C_{max} 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 C_{max} and AUC of dapagliflozin were up to 40% and 67% higher than matched healthy controls, respectively. FORXIGA should not be used in patients with severe hepatic impairment (see PRECAUTIONS).

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 populations has 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

Thirteen double-blind, randomised, controlled clinical trials were conducted with 6,362 subjects with type 2 diabetes to evaluate the efficacy and safety of FORXIGA; 4,273 subjects in these studies were treated with FORXIGA. Twelve studies had a treatment period of 24 weeks duration, 6 with long-term extensions ranging from 24 to 80 weeks (up to a total study duration of 104 weeks), and one study was 52 weeks in duration with long-term extensions of 52 and 104 weeks (total study duration of 208 weeks). Mean duration of diabetes ranged from 1.4 to 16.9 years. Fifty-one percent had mild renal impairment and 11% had moderate renal impairment. Fifty-one percent (51%) of the subjects were men, 83% were White, 9% were Asian, 3% were Black and 4% were of other racial groups. Eighty percent (80%) of the subjects had a body mass index (BMI) ≥27. Furthermore, two 12-week, placebo-controlled studies were conducted in patients with inadequately controlled type 2 diabetes and hypertension.

Monotherapy

A double-blind, placebo-controlled study of 24-week duration (with an additional extension period) was conducted to evaluate the safety and efficacy of monotherapy with FORXIGA in subjects with inadequately controlled type 2 diabetes mellitus. Once-daily treatment with FORXIGA resulted in statistically significant ($p < 0.0001$) reductions in HbA1c compared to placebo (Table 1).

In the extension period, HbA1c reductions were sustained through Week 102 (-0.61% and -0.17% adjusted mean change from baseline for FORXIGA 10 mg and placebo, respectively).

Table 1. Results at Week 24 (LOCF[a]) of a placebo-controlled study of FORXIGA as monotherapy

	Monotherapy	
	FORXIGA 10 mg	**Placebo**
N[b]	70	75
HbA1c (%)		
Baseline (mean)	8.01	7.79
Change from baseline[c]	-0.89	-0.23
Difference from placebo[c]	-0.66[*]	
(95% CI)	(-0.96, -0.36)	
Subjects (%) achieving: HbA1c <7%		
Adjusted for baseline	50.8[§]	31.6
Body weight (kg)		
Baseline (mean)	94.13	88.77
Change from baseline[c]	-3.16	-2.19
Difference from placebo[c]	-0.97	
(95% CI)	(-2.20, 0.25)	

[a] LOCF: Last observation (prior to rescue for rescued subjects) carried forward

[b] All randomised subjects who took at least one dose of double-blind study medication during the short-term double-blind period

[c] Least squares mean adjusted for baseline value

[*] p-value <0.0001 versus placebo

[§] Not evaluated for statistical significance as a result of the sequential testing procedure for secondary end points

Combination Therapy

FORXIGA was studied as add-on to metformin, add-on to a sulfonylurea (glimepiride), add-on to metformin and a sulfonylurea, add-on to a dipeptidyl peptidase 4 **(**DPP-4) inhibitor (sitagliptin) and add-on to insulin (with or without other antidiabetic therapies).

Initial Combination Therapy with Metformin

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 patients were treatment-naïve, 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.

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). 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
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.

Add-on combination therapy with other anti-hyperglycaemic agents

In a 52-week, active-controlled non-inferiority study (with 52- and 104-week extension periods), FORXIGA was evaluated as add-on therapy to metformin compared with a sulfonylurea (glipizide) as add-on therapy to metformin in subjects with inadequate glycaemic control (HbA1c >6.5% and ≤10%). The results showed a similar mean reduction in HbA1c from baseline to Week 52, compared to glipizide, thus demonstrating non-inferiority (Table 3). At Week 104, adjusted mean change from baseline in HbA1c was -0.32% for FORXIGA and -0.14% for glipizide. At Week 208, the secondary endpoint of adjusted mean change from baseline in HbA1c was -0.10% for FORXIGA and 0.20% for glipizide (see Fig 1). At 52, 104 and 208 weeks, a significantly lower proportion of subjects in the group treated with FORXIGA (3.5%, 4.3% and 5.0% respectively) experienced at least one event of hypoglycaemia compared to the group treated with glipizide (40.8%, 47.0% and 50.0% respectively). The proportions of subjects remaining in the study at Week 104 and at Week 208 were 56.2% and 39% respectively for the group treated with FORXIGA and 50.0% and 34.6% respectively for the group treated with glipizide.

Table 3. Results at Week 52 (LOCF[a]) in an active-controlled study comparing FORXIGA to glipizide as add-on to metformin

Parameter	FORXIGA +metformin	Glipizide +metformin
N[b]	400	401
HbA1c (%)		
Baseline (mean)	7.69	7.74
Change from baseline[c]	-0.52	-0.52
Difference from glipizide + metformin[c]	0.00[d]	
(95% CI)	(-0.11, 0.11)	
Body weight (kg)		
Baseline (mean)	88.44	87.60
Change from baseline[c]	-3.22	1.44
Difference from glipizide + metformin[c]	-4.65[*]	
(95% CI)	(-5.14, -4.17)	

[a]LOCF: Last observation carried forward

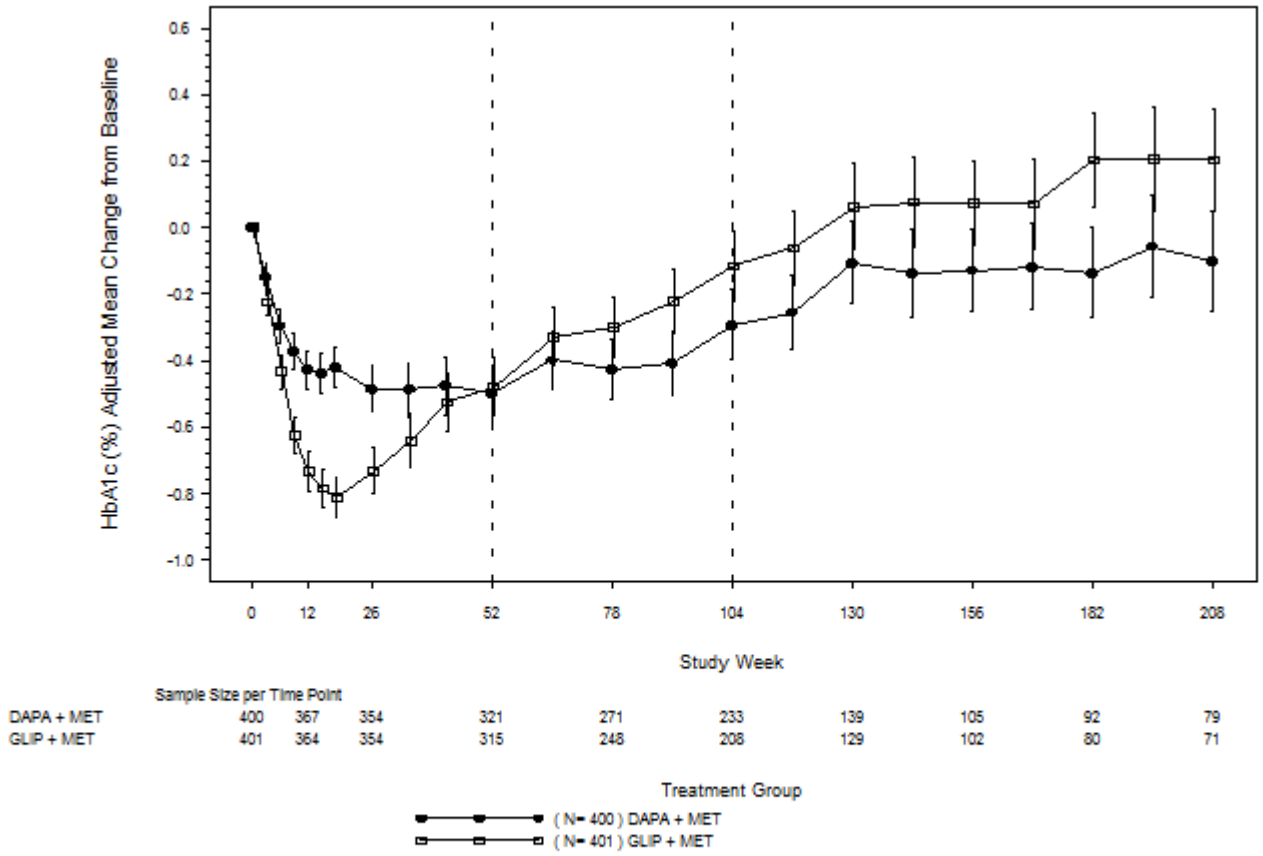
[b]Randomised and treated subjects with baseline and at least 1 post-baseline efficacy measurement

[c]Least squares mean adjusted for baseline value

[d]Non-inferior to glipizide + metformin

[*]p-value <0.0001

Figure 1: Adjusted Mean Change from Baseline Over Time in HbA1c (%) in a 208-Week Active-Controlled Study Comparing FORXIGA to Glipizide as Add-on to Metformin (Longitudinal Repeated Measures Analysis, Excluding Data after Rescue)



Subjects in the full analysis set.
Mean value based on repeated measures analysis model:
post-baseline = baseline treatment week week*treatment week*baseline.
Error bars represent 95% confidence intervals for the adjusted mean change from baseline.
Treatment symbols shifted horizontally to prevent error bar overlapping.

FORXIGA as an add-on with either metformin, glimepiride, metformin and a sulfonylurea, sitagliptin (with or without metformin) or insulin resulted in statistically significant reductions in HbA1c at 24 weeks compared with subjects receiving placebo ($p < 0.0001$; Tables 4,5 and 6).

Table 4. Results of 24-week (LOCF[a]) placebo-controlled studies of FORXIGA in add-on combination with metformin, or sitagliptin (with or without metformin)

	Add-on combination			
	Metformin[1]		DPP-4 Inhibitor (sitagliptin[2]) ±Metformin[1]	
	FORXIGA 10 mg	Placebo	FORXIGA 10 mg	Placebo
N[b]	135	137	223	224
HbA1c (%)				
Baseline (mean)	7.92	8.11	7.90	7.97
Change from baseline[c]	-0.84	-0.30	-0.45	0.04
Difference from placebo[c] (95% CI)	-0.54* (-0.74, -0.34)		-0.48* (-0.62, -0.34)	
Subjects (%) achieving: HbA1c <7%				
Adjusted for baseline	40.6**	25.9		
Body weight (kg)				
Baseline (mean)	86.28	87.74	91.02	89.23
Change from baseline[c]	-2.86	-0.89	-2.14	-0.26
Difference from placebo[c] (95% CI)	-1.97* (-2.63, -1.31)		-1.89* (-2.37, -1.40)	

[1]Metformin ≥ 1500 mg/day; [2]sitagliptin 100 mg/day

[a]LOCF: Last observation (prior to rescue for rescued subjects) carried forward

[b]All randomised subjects who took at least one dose of double-blind study medicinal product during the short-term double-blind period

[c]Least squares mean adjusted for baseline value

*p-value <0.0001 versus placebo + oral glucose-lowering medicinal product

**p-value <0.05 versus placebo + oral glucose-lowering medicinal product

Table 5. Results of 24-week placebo-controlled studies of dapagliflozin in add-on combination with sulfonylurea (glimepiride) or metformin and a sulfonylurea

	Add-on combination			
	Sulfonylurea (glimepiride[1])		Sulfonylurea + Metformin[2]	
	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo
N[a]	151	145	108	108
HbA1c (%)[b]				
Baseline (mean)	8.07	8.15	8.08	8.24
Change from Baseline[c]	-0.82	-0.13	-0.86	-0.17
Difference from Placebo[c]	-0.68*		−0.69*	
(95% CI)	(-0.86, -0.51)		(−0.89, −0.49)	
Subjects (%) achieving: HbA1c < 7% (LOCF)[d]				
Adjusted for baseline	31.7*	13.0	31.8*	11.1
Body weight (kg) (LOCF)[d]				
Baseline (mean)	80.56	80.94	88.57	90.07
Change from Baseline[c]	-2.26	-0.72	-2.65	-0.58
Difference from Placebo[c]	-1.54*		−2.07*	
(95% CI)	(-2.17, -0.92)		(−2.79, −1.35)	

[1] glimepiride 4 mg/day; [2]Metformin (immediate- or extended-release formulations) ≥1500 mg/day plus maximum tolerated dose, which must be at least half maximum dose, of a sulfonylurea for at least 8 weeks prior to enrollment.

[a] Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.

[b] Columns 1 and 2, HbA1c analyzed using LOCF (see footnote d); Columns 3 and 4, HbA1c analyzed using LRM (see footnote e)

[c] Least squares mean adjusted for baseline value

[d] LOCF: Last observation (prior to rescue for rescued subjects) carried forward

[e] LRM: Longitudinal repeated measures analysis

* p-value < 0.0001 versus placebo + oral glucose-lowering medicinal product(s)

Table 6. Results at Week 24 (LOCF[a]) in a placebo-controlled study of FORXIGA in combination with insulin (alone or with oral glucose-lowering medicinal products)

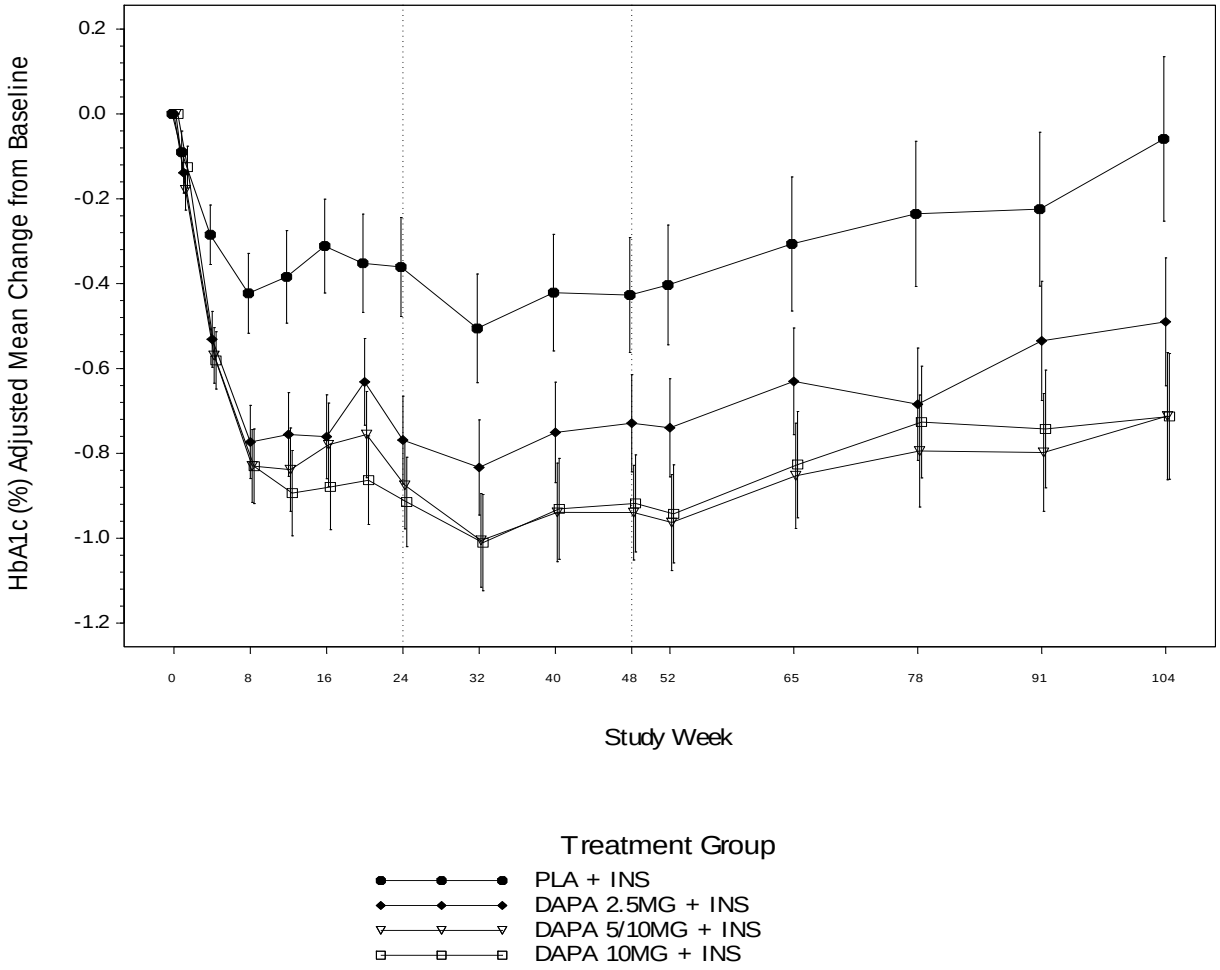
Parameter	FORXIGA 10 mg +insulin ±oral glucose-lowering medicinal products[2]	Placebo +insulin ±oral glucose-lowering medicinal products[2]
N[b]	194	193
HbA1c (%)		
Baseline (mean)	8.58	8.46
Change from baseline[c]	-0.90	-0.30
Difference from placebo[c]	-0.60[*]	
(95% CI)	(-0.74, -0.45)	
Body weight (kg)		
Baseline (mean)	94.63	94.21
Change from baseline[c]	-1.67	0.02
Difference from placebo[c]	-1.68[*]	
(95% CI)	(-2.19, -1.18)	
Mean daily insulin dose (IU)[1]		
Baseline (mean)	77.96	73.96
Change from baseline[c]	-1.16	5.08
Difference from placebo[c]	-6.23[*]	
(95% CI)	(-8.84, -3.63)	
Subjects with mean daily insulin dose reduction of at least 10% (%)	19.7[**]	11.0

[a]LOCF: Last observation (prior to or on the date of the first insulin up-titration, if needed) carried forward
[b]All randomised subjects who took at least one dose of double-blind study medicinal product during the short-term double-blind period
[c]Least squares mean adjusted for baseline value and presence of oral glucose-lowering medicinal product
[*]p-value <0.0001 versus placebo + insulin ±oral glucose-lowering medicinal product
[**]p-value <0.05 versus placebo + insulin ±oral glucose-lowering medicinal product
[1]Up-titration of insulin regimens (including short-acting, intermediate, and basal insulin) was only allowed if subjects met pre-defined FPG criteria.
[2]Fifty percent of subjects were on insulin monotherapy at baseline; 50% were on 1 or 2 oral glucose-lowering medicinal product(s) in addition to insulin: Of this latter group, 80% were on metformin alone, 12% were on metformin plus sulfonylurea therapy, and the rest were on other oral glucose-lowering medicinal products.

The reductions in HbA1c observed at Week 24 were sustained in add-on combination studies (glimepiride and insulin) with 48-week data (glimepiride) and up to 104-week data (insulin, see Fig 2). At Week 48 when added to sitagliptin (with or without metformin), the adjusted mean change from baseline for FORXIGA 10 mg and placebo was -0.30% and 0.38%, respectively. For the add-on to metformin study, HbA1c reductions were sustained through Week 102 (-0.78% and 0.02% adjusted mean change from baseline for 10 mg and placebo, respectively, see also Fig 3). At Week 104 for insulin (with or without additional oral glucose-lowering medicinal products), the HbA1c reductions were -0.71% and -0.06% adjusted mean change from baseline for FORXIGA 10 mg and placebo, respectively. At Weeks 48 and 104, the insulin

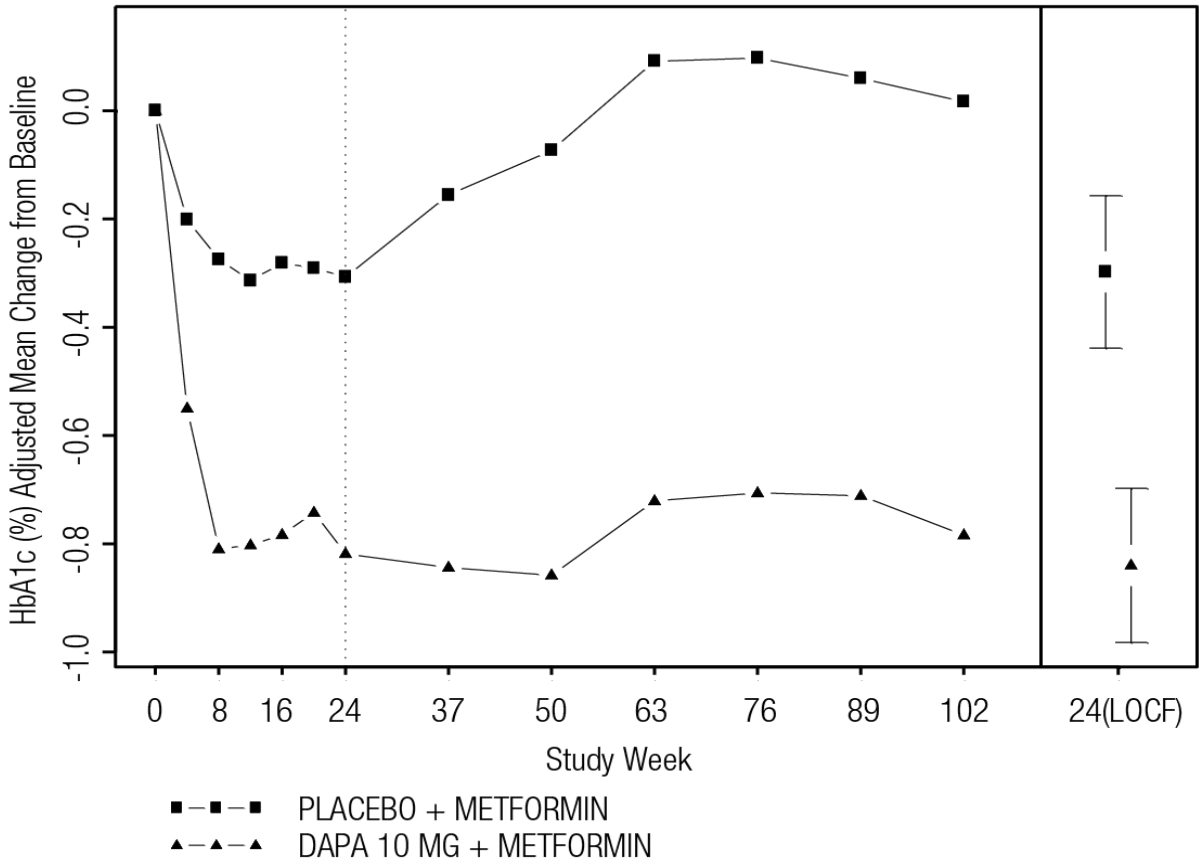
dose remained stable compared to baseline in subjects treated with FORXIGA 10 mg at an average dose of 76 IU/day (see Fig 4). In the placebo group there was a mean increase of 10.5 IU/day and 18.3 IU/day from baseline at Weeks 48 and 104, respectively. The proportion of subjects remaining in the study at Week 104 was 72.4% for the group treated with FORXIGA 10 mg and 54.8% for the placebo group.

Figure 2: 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 3: 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)

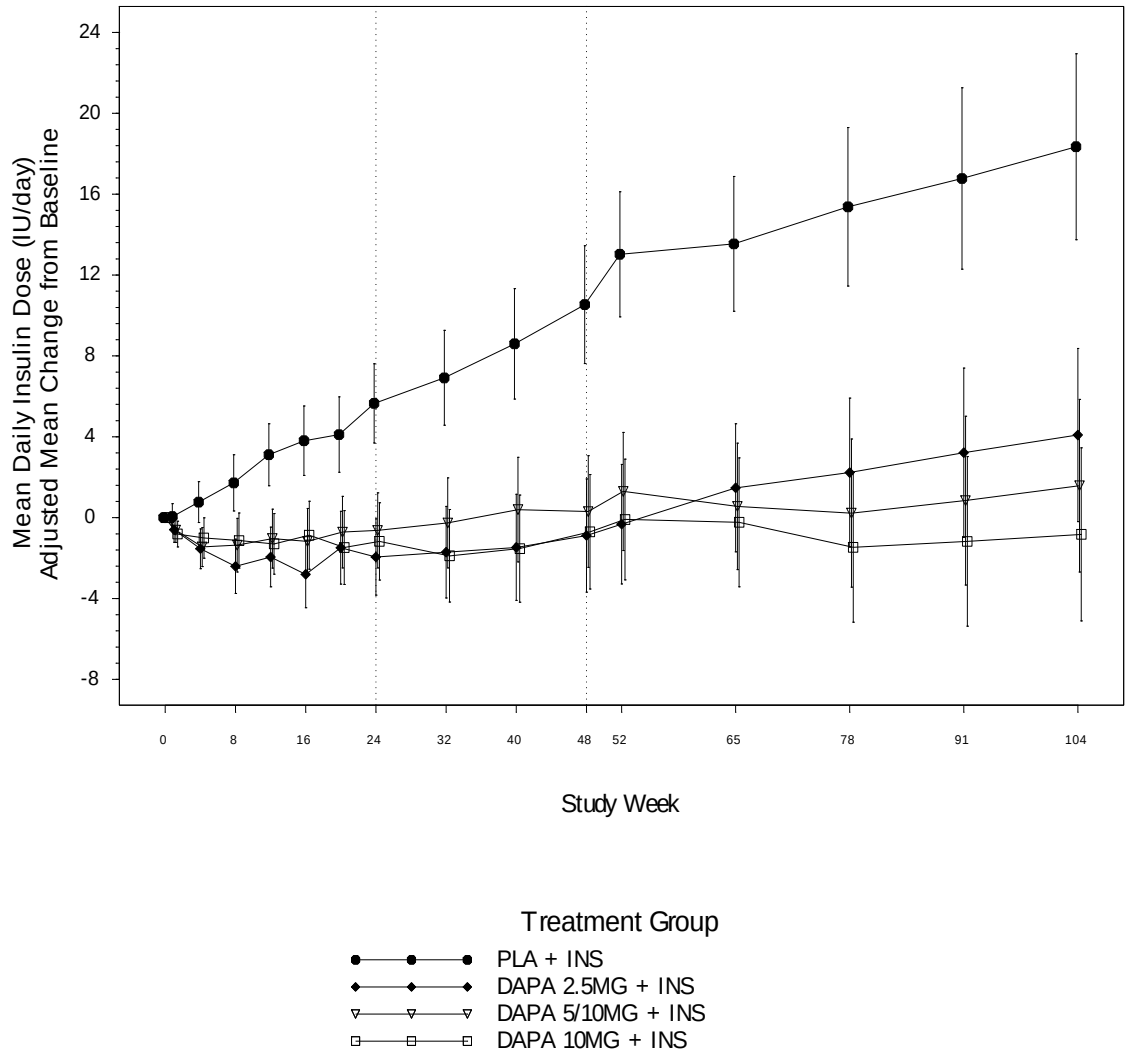


LOCF: Last observation (prior to rescue for rescued subjects) carried forward.

Values for 24 (OCF) 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.

Figure 4: 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

Fasting plasma glucose

Treatment with FORXIGA 10 mg as a monotherapy or as an add-on to either metformin, glimepiride, metformin and a sulfonylurea, sitagliptin (with or without metformin) or insulin resulted in statistically significant reductions in fasting plasma glucose (-1.90 to -1.20 mmol/L) compared to placebo (-0.33 to 0.21 mmol/L) at 24 weeks. This effect was observed at Week 1 of treatment and maintained in studies extended through Week 104.

Post-prandial glucose

Treatment with FORXIGA 10 mg as an add-on to glimepiride resulted in statistically significant reductions in 2-hour post-prandial glucose at 24 weeks that were maintained up to Week 48.

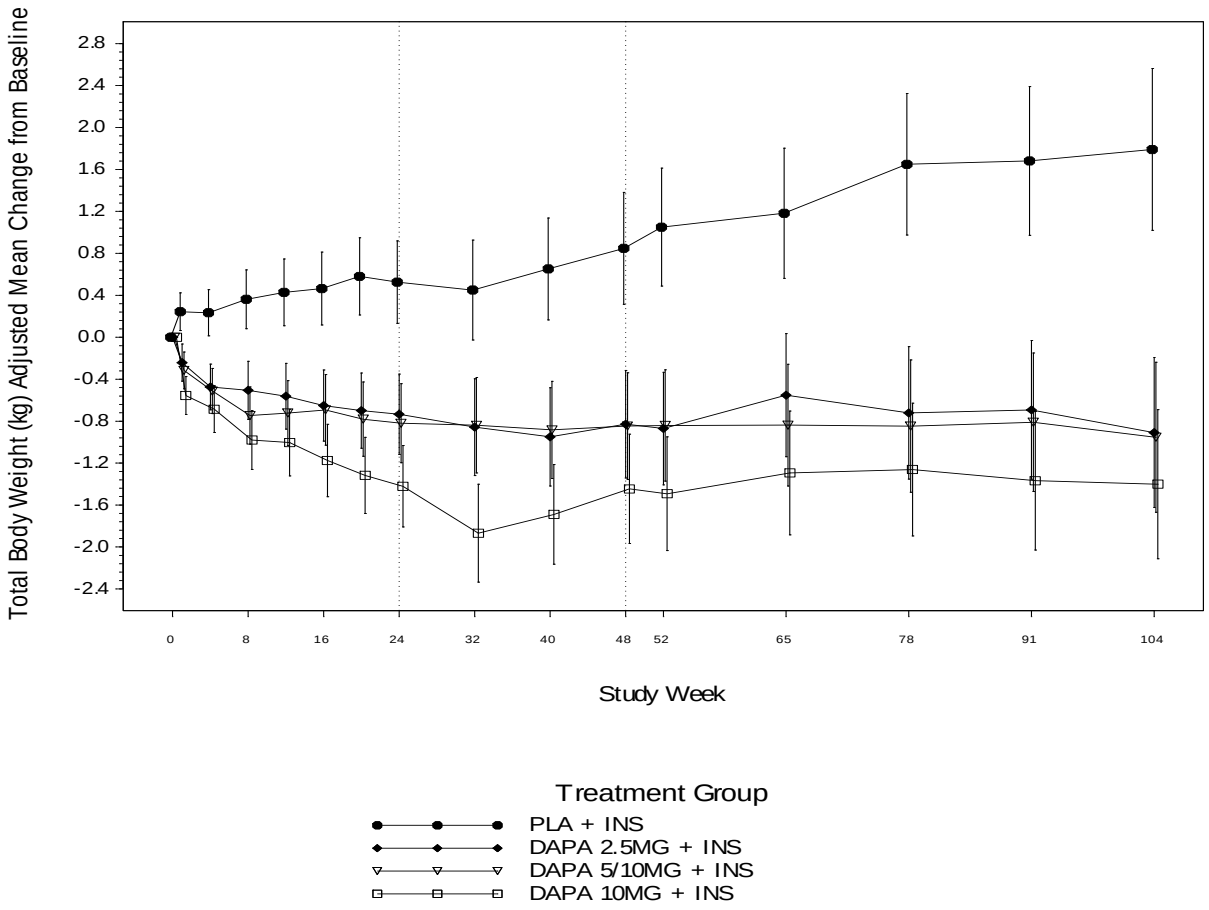
Treatment with FORXIGA 10 mg as an add-on to sitagliptin (with or without metformin) resulted in reductions in 2-hour post-prandial glucose at 24 weeks that were maintained up to Week 48.

Body weight

FORXIGA 10 mg as an add-on to metformin, glimepiride, metformin and a sulfonylurea, sitagliptin (with or without metformin) or insulin resulted in statistically significant body weight reduction at 24 weeks (p <0.0001, Tables 4, 5 and 6) with placebo-corrected reductions of 1.97 kg (2.43%), 1.54 kg (2.07%), 2.07 kg (2.25%), 1.89 kg (2.18%) and 1.68 kg (1.83%), respectively. These effects were sustained in longer-term trials (see Fig 5 for add-on to insulin). At 48 weeks, the difference for FORXIGA as add-on to sitagliptin (with or without metformin) compared with placebo was -2.22 kg. At 102 weeks, the difference for FORXIGA as add-on to metformin compared with placebo, or as add-on to insulin (at 104 weeks) compared with placebo was -2.14 and -2.88 kg, respectively.

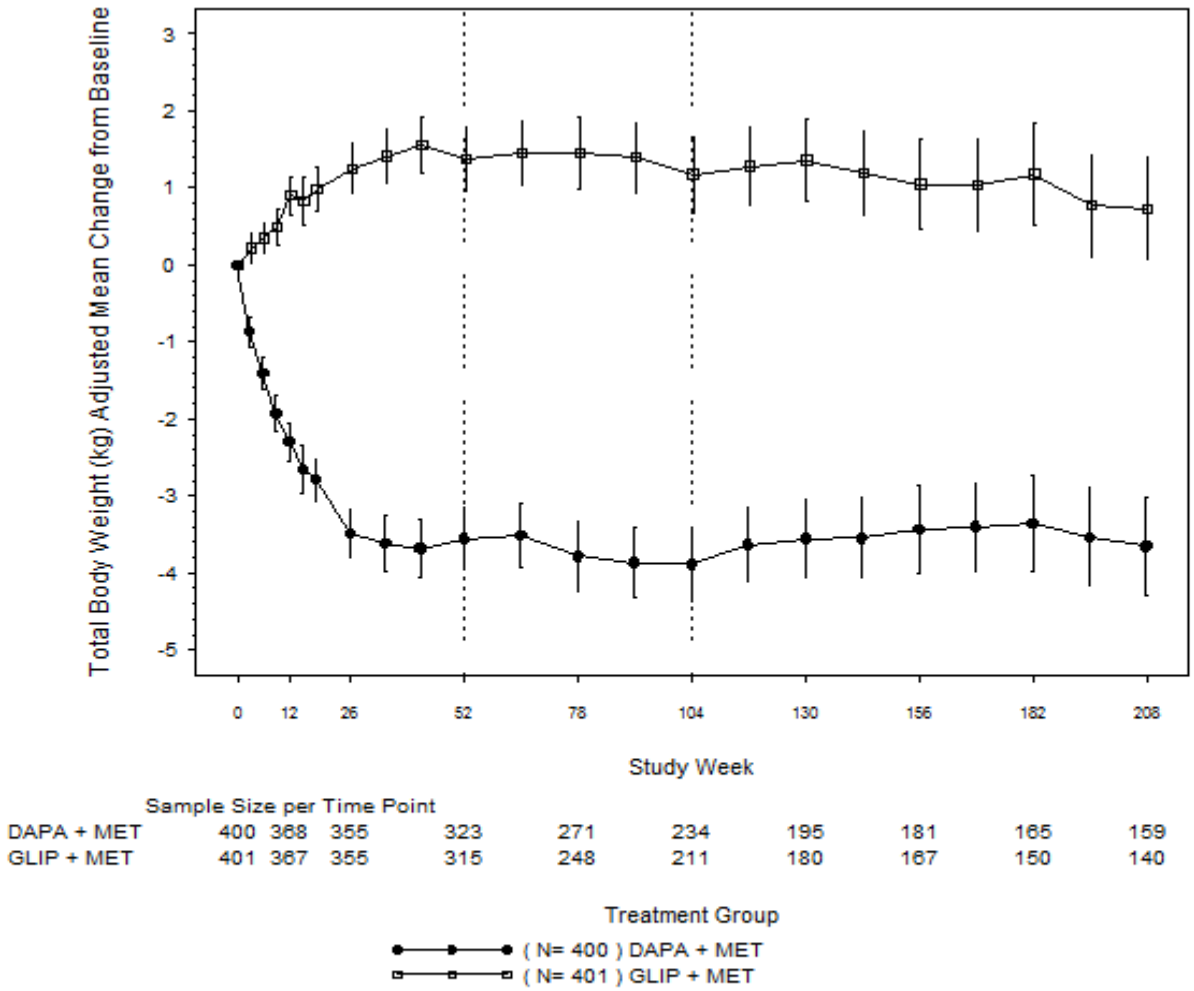
As an add-on therapy to metformin in an active-controlled non-inferiority study, FORXIGA resulted in a statistically significant body weight reduction compared with glipizide of -4.65 kg at 52 weeks (p <0.0001, Table 3) that was sustained at 104 and 208 weeks (-5.06 kg and -4.38 kg respectively) (see Fig 6).

Figure 5: 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

Figure 6: Adjusted Mean Change from Baseline Over Time in Body Weight (kg) in a 208-Week Active-Controlled Study Comparing FORXIGA to Glipizide as Add-on to Metformin (Longitudinal Repeated Measures Analysis, Excluding Data after Rescue)



Subjects in the full analysis set.
Mean value based on repeated measures analysis model:
post-baseline = baseline treatment week rescue week*treatment week*baseline.
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 glycaemic 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 CONTRAINDICATIONS and 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). These effects were sustained in a further extension of the study to 102 weeks where no important changes in BMD for the lumbar spine, femoral neck or total hip in either treatment group were observed.

Blood Pressure

In the pre-specified pooled analysis of 13 placebo-controlled studies (see ADVERSE EFFECTS), treatment with dapagliflozin 10 mg resulted in a systolic blood pressure change from baseline of –3.7 mmHg and diastolic blood pressure of –1.8 mmHg versus –0.5 mmHg systolic and -0.5 mmHg diastolic blood pressure for the placebo group at Week 24. Similar reductions were observed up to 104 weeks.

In two 12-week, placebo-controlled studies a total of 1,062 patients with inadequately controlled type 2 diabetes and hypertension (despite pre-existing stable treatment with an ACE-I or ARB in one study and an ACE-I or ARB plus one additional antihypertensive treatment in another study) were treated with FORXIGA 10 mg or placebo. At Week 12 for both studies, FORXIGA 10 mg plus usual antidiabetic treatment provided improvement in HbA1c, and decreased the placebo-corrected systolic blood pressure on average by 3.1 and 4.3 mmHg, respectively.

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 glycaemic control in patients with type 2 diabetes mellitus when diet and exercise have failed to provide adequate glycaemic 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 glycaemic control in combination with other anti-hyperglycaemic agents, when these together with diet and exercise,

do not provide adequate glycaemic control (see CLINICAL TRIALS and PRECAUTIONS for available data on different add-on combination therapies).

CONTRAINDICATIONS

Known hypersensitivity to any of the ingredients.

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

The pool of 21 double-blind, active and placebo-controlled studies (see ADVERSE EFFECTS) included 53% (4906/9339) 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 haemoglobin 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/1.73 m^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 persistently <60 mL/min/1.73 m^2 by MDRD or CrCl persistently<60 mL/min by Cockcroft-Gault). (See DOSING and ADMINISTRATION - Renal Impairment).

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, hypotension and/or electrolyte imbalances

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).

Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on antihypertensive therapy with a history of hypotension or elderly patients.

Ketoacidosis

There have been postmarketing reports of ketoacidosis, including diabetic ketoacidosis, in patients with type 1 and type 2 diabetes mellitus taking FORXIGA and other SGLT2 inhibitors, although a causal relationship has not been established. FORXIGA is not indicated for the treatment of patients with type 1 diabetes mellitus.

Patients treated with FORXIGA who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/l (250 mg/dL). If ketoacidosis is suspected, discontinuation or temporary interruption of FORXIGA should be considered and the patient should be promptly evaluated.

Predisposing factors to ketoacidosis include a low beta-cell function reserve resulting from pancreatic disorders (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), insulin

dose reduction, reduced caloric intake or increased insulin requirements due to infections, illness or surgery and alcohol abuse. FORXIGA should be used with caution in these patients. Consider assessing patients for ketoacidosis and temporarily discontinuing FORXIGA in clinical situations known to predispose to ketoacidosis.

Urinary Tract Infections

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalisation in patients receiving SGLT2 inhibitors, including FORXIGA. Urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to control in a placebo-pooled analysis up to 24 weeks (4.7% vs. 3.5%, respectively). Urinary glucose excretion may be associated with an increased risk of urinary tract infection. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (see ADVERSE EFFECTS). Temporary interruption of dapagliflozin should be considered when treating pyelonephritis or urosepsis. Discontinuation of dapagliflozin may be considered in cases of recurrent urinary tract infections; see ADVERSE EFFECTS.

Use with Medications Known to Cause Hypoglycaemia

Insulin and insulin secretagogues, such as sulfonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycaemia 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 adverse events related to renal impairment or failure compared with placebo. The most commonly reported adverse events related to renal function was increased blood serum creatinine increases, the majority of which were transient and reversible (see section PHARMACOLOGY – Pharmacokinetics and DOSAGE AND ADMINISTRATION).

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 events related to volume depletion (see section ADVERSE EFFECTS).

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

Combinations not studied

Dapagliflozin has not been studied in combination with glucagon like peptide 1 (GLP-1) analogues.

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.

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 21 clinical studies, FORXIGA use was not associated with an increased risk for adverse cardiovascular events (see section ADVERSE EFFECTS).

Cardiac failure

Experience in NYHA class I-II is limited, and there is no experience in clinical studies with dapagliflozin in NYHA class III-IV.

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.

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 and 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 rifampicin 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 C_{max} 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.

Rifampicin: Coadministration of a single dose of dapagliflozin (10 mg) and rifampicin (rifampicin), an inducer of various active transporters and drug-metabolizing enzymes, dosed to steady-state [600 mg/day] resulted in a decrease in dapagliflozin C_{max} 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 rifampicin coadministration (45 g). No dose adjustment of dapagliflozin is recommended when dapagliflozin is coadministered with rifampicin.

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 C_{max} 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 C_{max} of simvastatin but increased the AUC 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

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

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

Haematocrit

In the pool of 13 short-term placebo-controlled studies (see ADVERSE EFFECTS), increases from baseline in mean haematocrit values were observed in FORXIGA-treated patients starting at Week 1. At Week 24, the mean changes from baseline in haematocrit were −0.33% in the placebo group and 2.30% in the FORXIGA 10 mg group. By Week 24, haematocrit values >55% were reported in 0.4% of placebo-treated patients and 1.3% of FORXIGA 10 mg–treated patients.

In the pool of 9 placebo-controlled studies with short-term and long-term data, at week 102, the mean changes in haematocrit values were 2.68% vs. -0.46%, respectively. Results for haematocrit values >55% during the short-term plus long-term phase (the majority of patients were exposed to treatment for more than one year), were similar to week 24.

Most patients with marked abnormalities of elevated haematocrit or haemoglobin had elevations measured a single time that resolved at subsequent visits.

Serum Inorganic Phosphorus

In the pool of 13 short-term placebo-controlled studies, increases from baseline in mean serum phosphorus levels were reported at Week 24 in FORXIGA-treated patients compared with placebo-treated patients (mean increase of 0.042 mmol/L versus −0.0013 mmol/L, respectively). Higher proportions of patients with marked laboratory abnormalities of hyperphosphataemia (≥1.81 mmol/L for age 17-65 years or ≥1.65 mmol/L for age ≥66 years) were reported on FORXIGA at Week 24 (0.9% versus 1.7% for placebo and FORXIGA 10 mg, respectively).

In the pool of 9 placebo-controlled studies with short-term and long-term data, at week 102, reported increases in mean serum phosphorus were similar to week 24 results. During the short-term plus long-term phase laboratory abnormalities of hyperphosphataemia were reported in a higher proportion of patients in the FORXIGA group compared to placebo (3.0% vs. 1.6%, respectively). The clinical relevance of these findings is unknown.

Lipids

In the 13-study short-term placebo-controlled pool, small changes from baseline in mean lipid values were reported at week 24 in FORXIGA 10 mg treated patients compared with placebo (see ADVESE EFFECTS). Mean percent change from baseline at week 24 for FORXIGA 10 mg vs. placebo, respectively was as follows: total cholesterol 2.5% vs. 0.0%; HDL cholesterol 6.0% vs. 2.7%; LDL cholesterol 2.9% vs. -1.0%; triglycerides -2.7% vs. -0.7%. The ratio between LDL cholesterol and HDL cholesterol decreased for both treatment groups at week 24.

In the pool of 9 placebo-controlled studies with short-term and long-term data, the mean percent change from baseline at week 102 for FORXIGA 10 mg vs. placebo, respectively was as follows: total cholesterol 2.1% vs.-1.5%; HDL cholesterol 6.6% vs. 2.1%; LDL cholesterol 2.9% vs. -2.2%; triglycerides -1.8% vs. -1.8%.

Liver Function Tests

In the 21-study active and placebo-controlled pool (see ADVERSE EFFECTS), there was no imbalance across treatment groups in the incidence of elevations of ALT or AST. ALT >3 x ULN was reported in 1.2% of patients treated with FORXIGA 10 mg and 1.6% treated with comparator. ALT or AST >3 x ULN and bilirubin >2 x ULN was reported in 0.1% of patients on any dose of dapagliflozin, 0.2% of patients on FORXIGA, and 0.1% of patients on comparator.

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

Clinical Experience

Two major pools of patients were used to evaluate adverse effects with FORXIGA 10 mg versus control; a pool of 13 placebo-controlled studies and a larger pool comprised of 21 active- and placebo-controlled studies.

Placebo-controlled studies

The first pool is a pre-specified pool of patients from 13 short-term, placebo-controlled studies including the monotherapy studies, add-on studies, and the initial combination with metformin study. In the pool, 2360 patients were treated with FORXIGA 10 mg and 2295 were treated with placebo with a mean duration of exposure of 22 weeks.

The overall incidence of adverse events in patients treated with FORXIGA 10 mg was 60.0% compared to 55.7% for the placebo group. The incidence of discontinuation of therapy due to adverse events in patients who received FORXIGA 10 mg was 4.3% compared to 3.6% for the placebo group. The most commonly reported events leading to discontinuation and reported in at least 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%).

Active- and Placebo-Controlled Studies

The second pool is a pool of patients 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). These 21 studies provide a mean duration of exposure to FORXIGA 10 mg of 55 weeks (6247 patient-years).

The adverse reactions in the 13-study placebo-controlled pool reported (regardless of investigator assessment of causality) in ≥2% of patients treated with FORXIGA 10 mg and ≥1% more and at least 3 patients more than treated with placebo are shown in Table 7.

Table 7 Adverse reactions (Regardless of Investigator Assessment of Causality) in the 13 Placebo-Controlled Study Pool Reported in ≥2% of Patients Treated with FORXIGA 10 mg and ≥1% More Frequently than in Patients Treated with Placebo

	% of patients	
	FORXIGA 10 mg N=2360	**PLACEBO N=2295**
Infections and infestations		
Genital Infection[§]	5.5	0.6
Urinary tract infection*	4.7	3.5
Musculoskeletal and Connective Tissue Disorders		
Back pain	3.5	2.4
Renal and Urinary disorders		
Polyuria[¶]	3.3	1.2
Metabolism and nutrition disorders		
Hypoglycaemia[‡]	13.5	10.1

[§] 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.

* Urinary tract infection includes 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.

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

[‡] See heading 'Hypoglycaemia' 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 10 mg and 3.1% placebo).

Description of selected adverse events

Hypoglycaemia

The frequency of hypoglycaemia 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 hypoglycaemia with FORXIGA treatment than with placebo treatment (see section PRECAUTIONS).

In studies of FORXIGA used in monotherapy, add-on to metformin, and initial combination with metformin up to 102 weeks, there were no major episodes of hypoglycaemia reported. . In a study of FORXIGA added on to sitagliptin (with or without metformin) for up to 48 weeks, one major episode of hypoglycaemia was reported in a patient treated with FORXIGA 10 mg plus sitagliptin (without metformin). In these studies, the frequency of minor episodes of hypoglycaemia was similar (<5%) across the treatment groups, including placebo.

In a study with FORXIGA 10 mg added on to glimepiride for up to 48 weeks that also included other doses of dapagliflozin, one episode of major hypoglycaemia in a patient in the dapagliflozin 2.5 mg plus glimepiride group was reported. Minor episodes of hypoglycaemia were reported in 7.9% of patients in the FORXIGA 10 mg plus glimepiride group and 2.1% patients in the placebo plus glimepiride group.

In an add-on to metformin study that compared dapagliflozin to glipizide up to 104 weeks, there were 3 episodes of major hypoglycaemia in the glipizide plus metformin group and none in the FORXIGA plus metformin group. Minor episodes of hypoglycaemia were reported in 2.5% of subjects in the dapagliflozin plus metformin group and 42.4% of subjects in the glipizide plus metformin group.

In an add-on to metformin and a sulfonylurea study, up to 24 weeks, no episodes of major hypoglycaemia were reported. Minor episodes of hypoglycaemia were reported in 12.8% of subjects who received dapagliflozin 10 mg plus metformin and a sulfonylurea and in 3.7% of subjects who received placebo plus metformin and a sulfonylurea.

In an add-on to insulin study up to 24 weeks, episodes of major hypoglycaemia were reported in 1 (0.5%) and 1 (0.5%) patient in FORXIGA 10 mg plus insulin and placebo plus insulin groups, respectively. Up to 104 weeks, 2 (1.0%) and 1 (0.5%) patients in FORXIGA 10 mg plus insulin and placebo plus insulin groups reported major episodes. Up to 24 weeks, 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. Up to 104 weeks, minor episodes were reported in 104 [53.1%] patients for FORXIGA 10 mg plus insulin and 82 [41.6%] patients for placebo. Patients in this study could also be treated with a maximum of two oral anti-diabetes medications (OADs) including metformin.

Volume depletion

In the pooled analysis of 13 short-term, placebo-controlled studies, events related to volume depletion (including reports of dehydration, hypovolemia or hypotension) were reported in 1.1% and 0.7% of patients who received FORXIGA 10 mg and placebo respectively. Across the pool of 21 active and placebo-controlled studies, serious events occurred in ≤0.2% of patients and were balanced between FORXIGA 10 mg and comparator (see section PRECAUTIONS).

Genital Infections

In the pooled analysis of 13 short-term, placebo-controlled studies, events of genital infections were reported in 5.5% and 0.6% of patients who received FORXIGA 10 mg and placebo respectively,. 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% placebo). Subjects with a history of recurrent genital infection were more likely to

experience an infection. Infections were more frequently reported in females (8.4% FORXIGA 10 mg vs. 1.2% placebo) than in males (3.4% FORXIGA 10 mg vs. 0.2% placebo). The most frequently reported genital infections were vulvovaginal mycotic infections in females, and balanitis in males.

In 9 of the 13 studies in the placebo-controlled pool, long-term data was available. In this short-term plus long-term placebo-pooled analysis (mean duration of treatment was 439.5 days for FORXIGA 10 mg and 419.0 days for placebo); the proportions of patients with events of genital infections were 7.7% (156/2026) in the FORXIGA 10 mg group and 1.0% (19/1956) in the placebo group. Of the patients treated with FORXIGA 10 mg who experienced an infection, 67.9% had only one and 10.9% had 3 or more. Of the patients treated with placebo who experienced an infection, 89.5% had only one and none had 3 or more.

Urinary Tract Infections

In the pooled analysis of 13 short-term, placebo-controlled studies, events of urinary tract infections were reported in 4.7% and 3.5% of patients who received FORXIGA 10 mg and placebo, respectively. Most 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 (0.2% FORXIGA 10 mg vs. 0.1% placebo). Subjects with a history of recurrent urinary tract infection were more likely to experience an infection. Infections were more frequently reported in females (8.5% FORXIGA 10 mg vs. 6.7% placebo) than in males (1.8% FORXIGA 10 mg vs. 1.3% placebo) (see section PRECAUTIONS).

In the short-term plus long-term placebo-pooled analysis of 9 short-term studies with long term data available, the proportions of patients with events of urinary tract infections were 8.6% in the FORXIGA 10 mg group and 6.2% in the placebo group. Of the patients treated with FORXIGA 10 mg who experienced an infection, 77.6% had only one and 6.3% had 3 or more. Of the patients treated with placebo who experienced an infection, 77.7% had only one and 9.9% had 3 or more.

Events related to decreased renal function

In the 13 study, short-term, placebo controlled pool, adverse effects related to increased creatinine were grouped (e.g. decreased renal creatinine clearance, renal impairment, increased blood creatinine and decreased glomerular filtration rate). This grouping of reactions was reported in 3.2% and 1.8% of patients who received dapagliflozin 10 mg and placebo, respectively. In patients with normal renal function or mild renal impairment (baseline eGFR ≥60 mL/min/1.73m^2) this grouping of reactions were reported in 1.3% and 0.8% of patients who received dapagliflozin 10 mg and placebo, respectively. These reactions were more common in patients with baseline eGFR ≥30 and <60 mL/min/1.73m^2 (18.5% dapagliflozin 10 mg vs 9.3% placebo).

Further evaluation of patients who had renal-related adverse events showed that most had serum creatinine changes of ≤44 µmol/L from baseline. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment.

Malignancies

During clinical trials, the overall proportion of subjects with malignant or unspecified tumours was similar between those treated with FORXIGA (1.50%) and placebo/comparator (1.50%),

and there was no carcinogenicity or mutagenicity signal in animal data (see PRECAUTIONS). 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, 34.4% of subjects had a history of cardiovascular disease (excluding hypertension) at baseline and 67.9% 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 1.62% per patient-year in patients treated with FORXIGA and 2.06% in comparator-treatment patients, per patient-year. The hazard ratio comparing FORXIGA to comparator was 0.79 (95% confidence interval: 0.58, 1.07), 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 0.77 (95% CI: 0.54, 1.10).

Postmarketing experience

The following post-marketing case reports have been reported during post-approval use of FORXIGA. Because these cases are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency.

Metabolism and nutrition disorders – Ketoacidosis

Infections and infestations – Pyelonephritis, urosepsis

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, a DPP4 inhibitor (with or without metformin), or insulin (alone or with one or both of metformin or a sulfonylurea [SU]). When FORXIGA is used as an add-on therapy with insulin or an insulin secretagogue (e.g sulfonylurea), a lower dose of insulin or an insulin secretagogue may be considered to reduce the risk of hypoglycaemia.

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 glycaemic 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 persistently <60 mL/min/1.73 m^2 by MDRD or CrCl persistently <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 hypoglycaemia 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 hypoglycaemia 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

AstraZeneca Pty Ltd
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Alma Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (Schedule 4).

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

22 October 2012

DATE OF MOST RECENT AMENDMENT

22 February 2016