For the use of a registered medical practitioner or a hospital or a laboratory only

AstraZeneca

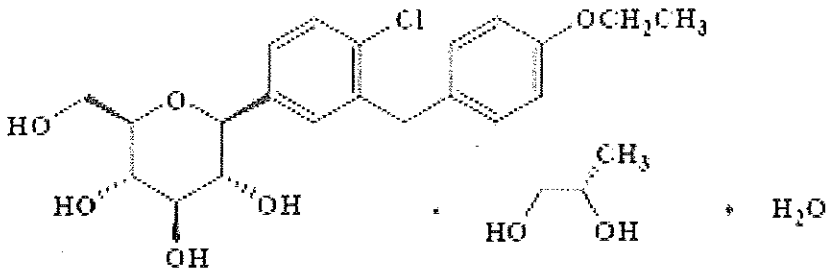
# Dapagliflozin Tablets

# Forxiga™ 5mg and 10mg

## 1. DESCRIPTION

FORXIGA (dapagliflozin propanediol) is a potent, highly selective and orally active inhibitor of the human renal sodium-glucose cotransporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption.

Dapagliflozin propanediol is described chemically as D-glucitol, 1,5-anhydro-1-*C*-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1*S*)-, compounded with (2*S*)-1,2-propanediol, hydrate (1:1:1). 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:




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

**Composition:**

1. Dapagliflozin propanediol monohydrate equivalent Dapagliflozin : 10 mg
   Titanium Dioxide IP & Iron oxide yellow Ph.Eur.

2. Dapagliflozin propanediol monohydrate equivalent Dapagliflozin : 5 mg
   Titanium Dioxide IP & Iron oxide yellow Ph.Eur.

## 2. THERAPEUTIC INDICATIONS

**Monotherapy:** FORXIGA is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.

**Add-on combination:** FORXIGA is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin, a thiazolidinedione, a sulfonylurea, a DPP4 inhibitor (with or without metformin), or insulin (alone or with up to two oral antidiabetic medications) when the existing therapy, along with diet and exercise, does not provide adequate glycemic control.

**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 dual dapagliflozin and metformin therapy is appropriate.

AstraZeneca

FORXIGA is not indicated for use in patients with type 1 diabetes.

FORXIGA should not be used for the treatment of diabetic ketoacidosis

FORXIGA should not be used in patients with moderate to severe renal impairment (estimated glomerular filtration rate [eGFR] persistently < 45 mL/min/1.73 $m^2$ as calculated by the Modification of Diet in Renal Disease [MDRD] formula, or creatinine clearance [CrCl] persistently ≤ 60 mL/min as calculated by Cockcroft-Gault formula) or end stage renal disease (ESRD).

# 3. POSOLOGY AND METHOD OF ADMINISTRATION

## 3.1 Recommended Dosage

The recommended dose of FORXIGA is 10 mg taken once daily at anytime 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 thiazolidinedione, a sulfonylurea, a DPP4-inhibitor (with or without metformin), or insulin (with or without oral antidiabetic therapy, either metformin plus insulin dual therapy or metformin plus sulfonylurea plus insulin triple therapy).

**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 dose should further have their metformin dose increased according to approved local label guidelines.

## 3.2 Renal Impairment

No dosage adjustment for FORXIGA is indicated based on renal function

The efficacy of FORXIGA is dependent on renal function. FORXIGA should not be used in patients with moderate to severe renal impairment (defined as eGFR persistently <45 mL/min/1.73 $m^2$ by MDRD or CrCl persistently <60 mL/min by Cockcroft-Gault) or ESRD (see sections 5.1,5.10, and 7.1).

## 3.3 Hepatic Impairment
No dosage adjustment for FORXIGA is necessary for patients with mild, moderate, or severe hepatic impairment (see section 9.3).

## 3.4 Pediatric and Adolescent
Safety and effectiveness of FORXIGA in pediatric and adolescent patients have not been established.

## 3.5 Geriatric
No dosage adjustment for FORXIGA is required based on age (see section 5.8).

AstraZeneca

### 3.6 Patients at Risk for Volume Depletion

For patients at risk for volume depletion due to co-existing conditions, a 5-mg starting dose of FORXIGA may be appropriate (see sections 5.2 and 7.1).

## 4 CONTRAINDICATIONS

FORXIGA is contraindicated in patients with a history of any serious hypersensitivity reaction to the active substance or to any of the excipients.

## 5 WARNINGS AND PRECAUTIONS FOR USE

### 5.1 Use in Patients with Renal Impairment

The efficacy of FORXIGA is dependent on renal function.

FORXIGA should not be used in patients with moderate to severe renal impairment (defined as eGFR persistently <45 mL/min/1.73 $m^2$ by MDRD or CrCl persistently <60 mL/min by Cockcroft-Gault) or ESRD. Therefore, as in all diabetic patients, renal function should be evaluated prior to initiation of FORXIGA and periodically thereafter (see section 3.2, 5.10, and 7.1).

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, therefore, should not be used in this population.

### 5.2 Use in Patients at Risk for Volume Depletion

The diuretic effect of FORXIGA decreases intravascular volume. For patients at risk for volume depletion or dehydration due to co-existing conditions (such as patients with extremely poor glycemic control, elderly patients and those on concomitant diuretics), a 5-mg starting dose of FORXIGA may be appropriate. These patients should also be instructed to take water appropriately and carefully monitored. If such symptoms as dry mouth, polyuria, pollakiuria, and blood pressure decreases are observed and dehydration is suspected, appropriate measures including fluid replacement or temporary interruption of FORXIGA should be considered. (see section 7.1). Additionally, there has been limited information from SGLT2 inhibitor postmarketing reports of cases of thromboembolism including cerebral infarction, secondary to dehydration, therefore caution should be fully excercised.

### 5.3 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 hypoglycaemia when used in combination with FORXIGA (see section 7.1).

### 5.4 Pregnancy and Lactation

**Pregnancy**

FORXIGA must not be used in the second and third trimesters of pregnancy. In the time period corresponding to the second and third trimesters of pregnancy with respect to human renal maturation, maternal exposure to dapagliflozin in rat studies was associated with

increased incidence and/or severity of renal pelvic and tubular dilatation in progeny (see section 11.1).

In conventional studies of embryo-fetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the first trimester period of non-renal organogenesis in humans. No developmental toxicities were observed in rabbits at any dose tested (1191× the maximum recommended human dose [MRHD]).In rats, dapagliflozin was neither embryolethal nor teratogenic (1441× the MRHD) in the absence of maternal toxicity.

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

## Lactation

FORXIGA must not be used by a nursing woman. Studies in rats have shown excretion of FORXIGA in milk. Direct and indirect exposure of FORXIGA to weanling juvenile rats and during late pregnancy are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny, although the long-term functional consequences of these effects are unknown. These periods of exposure coincide with a critical window of renal maturation in rats. As functional maturation of the kidneys in humans continues in the first 2 years of life, FORXIGA-associated dilated renal pelvis and tubules noted in juvenile rats could constitute potential risk for human renal maturation during the first 2 years of life. Additionally, the negative effects on body-weight gain associated with lactational exposure in weanling juvenile rats suggest that FORXIGA must be avoided during the first 2 years of life (see section 11.1).

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

## 5.5 Labor and Delivery

## 5.6 Pediatric Use

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

## 5.7 Geriatric Use

No dosage changes of FORXIGA are recommended based on age. A total of 2403 (26%) of the 9339 treated patients were 65 years and older and 327 (43.5%) patients were 75 years and older in the pool of 21 double-blind, controlled, clinical safety and efficacy studies of FORXIGA. After controlling for level of renal function (eGFR), there was no conclusive evidence suggesting that age is an independent factor affecting efficacy. Overall, the proportion of patients reporting adverse events was consistent between those ≥65 and <65 years of age. In patients ≥65 years of age, a higher proportion of patients treated with FORXIGA had events related to renal impairment or failure compared with placebo. The most commonly reported adverse events related to renal impairment or failure in patients ≥65 years of age for any treatment group were creatinine renal clearance decreased, renal impairment, and increased blood creatinine.

Older patients are more likely to have impaired renal function. The renal function recommendations provided for all patients also apply to elderly patients (see section 5.1, 5.11, and 7.1).

## 5.9 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with FORXIGA or any other antidiabetic drug. In a meta-analysis of 21 clinical studies, FORXIGA use was not associated with an increased risk for adverse cardiovascular events (see section 7.1).

## 5.10 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.

## 5.11 Renal Impairment

***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, clinical safety and efficacy studies 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 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/1.73 $m^2$)***

The pool of 21 active- and placebo-controlled clinical studies included 11% (1055/9339) 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/1.73 $m^2$). The mean change from baseline in HbA1c and the placebo-corrected mean HbA1c change 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 study of diabetic patients with moderate renal impairment (252 patients with mean eGFR 45 mL/min/1.73 $m^2$). 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/1.73$m^2$) in this study was conducted at Week 24. In patients with baseline eGFR ≥45 to <60 mL/min/1.73 $m^2$, 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/1.73 $m^2$ in this study, the mean change from baseline in HbA1c and the placebocorrected 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 section 9.2).

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/1.73 m2); 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 program of clinical studies 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 PTH and serum phosphorus observed with FORXIGA in the overall program of clinical studies 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.

Safety was also assessed in the moderate renal impairment study. At at Week 52, FORXIGA was associated with changes from baseline in mean eGFR and eCrCl (eGFR: FORXIGA 10 mg −4.46 mL/min/1.73 m2 and placebo −2.58 mL/min/1.73 m2) (eCrCl: FORXIGA 10 mg −7.27 mL/min and placebo −2.56 mL/min). At Week 104, these changes persisted (eGFR: FORXIGA 10 mg −3.50 mL/min/1.73m2 and placebo −2.38 mL/min/1.73 m2) (eCrCl: FORXIGA 10 mg −6.32 mL/min and placebo −2.35 mL/min)
With FORXIGA 10 mg, these eGFR and eCrCl reductions were evident at week 1 and remained stable through Week 104 while placebo-treated patients had a slow continuous decline through Week 52 that stabilized through Week 104.

At Week 52 and persisting through Week 104,, greater increases in mean parathyroid hormone (PTH) and serum phosphorus were observed in this study with FORXIGA 10 mg compared to placebo, where baseline values of these analytes were higher. Elevations of potassium of ≥6 mEq/L were more common in patients treated with placebo (12.0%) than those treated with FORXIGA 5 mg and 10 mg (4.8% for both groups) during the cumulative 104-week treatment period.50 The proportion of patients discontinued for elevated potassium, adjusted for baseline potassium, was higher for the placebo group (14.3%) than for the FORXIGA groups (6.9% and 6.7% for the 5 mg and 10 mg groups, respectively)

Overall, there were 13 patients with an adverse event of bone fracture reported in this study up to Week 104 of which 8 occurred in the FORXIGA 10 mg group, 5 occurred in the FORXIGA 5 mg group, and none occurred in the placebo group. Eight (8) of these 13 fractures were in patients who had eGFR 30 to 45 mL/min/1.73 m2 and 11 of the 13 fractures
were reported within the first 52 weeks. There was no apparent pattern with respect to the site of fracture.

### *Patients with Severe Renal Impairment (eGFR <30 mL/min/1.73 $m^2$)*

Patients with severe renal impairment (eGFR <30 mL/min/1.73$m^2$), or ESRD, were not included in clinical studies. Based on its mechanism of action, FORXIGA was not anticipated to be effective in these populations.

## 5.12 Use in Patients with Diabetes and Cardiovascular Disease

In two 24-week, placebo-controlled studies with 80-week extension periods, a total of 1887 patients with type 2 diabetes and cardiovascular disease (CVD) were treated with FORXIGA 10 mg or placebo. Patients with established CVD and inadequate glycemic control (HbA1c ≥7.0% and ≤10.0%), despite pre-existing, stable treatment with oral antidiabetic therapy (OADs) or insulin (alone or in combination) prior to entry, were eligible for these studies and were stratified according to age (<65 years or ≥65 years), insulin use (no or yes), and time from most recent qualifying cardiovascular event (>1 year or <1 year prior to enrollment).

Across the 2 studies, 942 patients were treated with FORXIGA 10 mg and 945 with placebo. Ninety-six percent (96%) of patients treated with FORXIGA across the 2 studies had hypertension at entry, the majority for more than 10 years duration; the most common qualifying cardiovascular events were coronary heart disease (75%) or stroke (22%).

Approximately 19% of patients received loop diuretics at entry and 15% had congestive heart failure (2% had NYHA Class III). Approximately 37% of patients treated with FORXIGA 10 mg also received metformin plus one additional OAD at entry, (sulfonylurea,thiazolidinedione, DPP4-inhibitor, or other OAD with or without insulin at entry) 39% received insulin plus at least one OAD, and 18% received insulin alone.

Treatment with FORXIGA 10 mg as add-on to pre-existing antidiabetic treatments over 24 weeks provided significant improvement in co-primary endpoints of HbA1c and composite clinical benefit compared with placebo in this population. Significant reductions in total body weight and seated systolic blood pressure were also seen (see section 10.3). These benefits extended up to 104 weeks of treatment The safety profile of FORXIGA in these studies was consistent with that of FORXIGA in the general clinical study population through 104 weeks of treatment (see section 7.1).

# 6 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

The metabolism of dapagliflozin is primarily mediated by UGT1A9-dependent glucuronide conjugation.The major metabolite, dapagliflozin 3-O-glucuronide, is not an SGLT2 inhibitor.

In *in vitro* studies, dapagliflozin and dapagliflozin 3-O-glucuronide neither inhibited CYP 1A2, 2C9, 2C19, 2D6, 3A4, nor induced CYP1A2, 2B6 or 3A4. Therefore, dapagliflozin is not expected to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes, and drugs that 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.

## 6.1 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, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin. Following coadministration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolizing enzymes) or mefenamic acid (an inhibitor of UGT1A9), a 22% decrease and a 51% increase, respectively, in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion in either case.

*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.

*Voglibose (α-glucosidase inhibitor):* Coadministration of a single dose of dapagliflozin (10 mg) and voglibose (0.2 mg three times per day) did not alter the pharmacokinetics of dapagliflozin.

*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.

*Rifampin:* Coadministration of a single dose of dapagliflozin (10 mg) and rifampin (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 hours following administration of dapagliflozin alone (51 g) was not markedly affected by rifampin coadministration (45 g). No dose adjustment of dapagliflozin is recommended when dapagliflozin is coadministered with rifampin.

*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 mefanamic acid.

## 6.2 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 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 Pgp– 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]).

## 6.3 Other Interactions

The effects of smoking, diet, herbal products, and alcohol use on the pharmacokinetics of

dapagliflozin have not been specifically studied.

AstraZeneca

# 7 UNDESIRABLE EFFECTS

## 7.1 Clinical Experience

Two major pools of patients were used to evaluate adverse reactions with FORXIGA 10 mg versus control, a placebo-controlled study pool and a larger pool of active- and placebocontrolled studies.

**Placebo-Controlled Studies**

The first pool is a prespecified pool of patients from 13 short-term, placebo-controlled studies used to evaluate and present all safety data other than malignancies, liver tests, and hypoglycemia (evaluated by individual study).This pool included the monotherapy studies, several add-on studies (metformin, sulfonylurea, pioglitazone, DPP4-inhibitor, insulin, and two studies with a combination of add-on therapies), and an initial combination with metformin study. Across these 13 studies, 2360 patients were treated once daily with FORXIGA 10 mg and 2295 were treated with placebo (either as monotherapy or in combination with other antidiabetic therapies).

These 13 studies provide a mean duration of exposure of 22 weeks. The mean age of the population was 59 years and 4% were older than 75 years. Fifty-eight percent (58%) of the population was male; 84% were White, 9% were Asian, and 3% were Black or African American. At baseline, the population had diabetes for an average of 9 years, mean HbA1c was 8.2%, and renal function was normal or mildly impaired in 88% of patients and moderately impaired in 11% of patients.

**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).81 Across both treatment groups, the mean age of the population was 58 years and 3.5% were older than 75 years. Fifty-six percent (56%) of the population was male; 77% were White, 16% were Asian, and 4% were Black or African American. At baseline, the population had diabetes for an average of 7 years, 34% of patients had a history of cardiovascular disease, mean HbA1c was 8.2%, and baseline renal function was normal or mildly impaired in 89% of patients and moderately impaired in 11% of patients.

Additionally, FORXIGA 5 mg was evaluated in a 12-study, short-term, placebo-controlled pool of patients that included 1145 patients treated with FORXIGA 5 mg as monotherapy or in combination with other antidiabetic therapy (mean exposure = 22 weeks) and 1393 patients treated with placebo as monotherapy or in combination with other antidiabetic therapy (mean exposure = 21 weeks). All safety data presented for FORXIGA 5 mg is from this pool.

The overall incidence of adverse events for the 13-study, short-term, placebo-controlled pool (short-term treatment) in patients treated with FORXIGA 10 mg was 60.0% compared to

55.7% for the placebo group.85 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%).

The adverse reactions in this 13-study placebo-controlled pooled analysis 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 1

**Table 1: 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 (Excluding Hypoglycemia)[*,†]**

| **System Organ Class**<br>Preferred Term | **FORXIGA 10 mg**<br>**N=2360** |
|---|---|
| *Infections and Infestations*<br>Genital infection[‡] | Common |
| *Infections and Infestations*<br>Urinary tract infection[§] | Common |
| *Musculoskeletal and Connective Tissue Disorders*<br>Back pain | Common |
| *Metabolism and Nutrition Disorders*<br>Polyuria[¶] | Common |

* The 13 placebo-controlled studies included 3 monotherapy, 1 initial combination with metformin, 2 add-on to metformin, 2 add-on to insulin, 1 add-on to pioglitazone, 1 add-on to sitagliptin, 1 add-on to glimepiride, and 2 studies with combination add-on therapy. Table shows up to 24-week (short-term) data regardless of glycemic rescue.

† For hypoglycemia information see Hypoglycemia subsection.

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

§ 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.

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 or more patients treated with FORXIGA 10 mg, and regardless of relationship to FORXIGA as reported by investigator, are described below by treatment regimen.

AstraZeneca

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

In an add-on to thiazolidinedione study: nasopharyngitis (7.9% FORXIGA 10 mg and 3.6% placebo), diarrhea (6.4% FORXIGA 10 mg and 4.3% placebo)

**Volume depletion**
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, in the 13-study, short-term, placebo-controlled pool. Serious events occurred in ≤ 0.2% of patients across the 21 active- and placebo-controlled studies and were balanced between FORXIGA 10 mg and comparator. In subgroup analyses of patients on loop diuretics or ≥65 years of age in the 13-study placebo-controlled pool, the proportion of patients with events related to volume depletion were slightly higher in patients treated with FORXIGA 10 mg than in those treated with placebo (events in patients on loop diuretics:
2.5% vs 1.5%; events in patients ≥ 65 years of age: 1.7% vs 0.8%, respectively).

Events related to volume depletion were reported in 0.6% of patients who received FORXIGA 5 mg compared with 0.4% who received placebo in the 12-study, short-term, placebo-controlled pool.95 No patients on loop diuretics and only 1 patient ≥ 65 years of age (0.5%) had an event related to volume depletion during treatment with FORXIGA 5 mg compared with 1 patient on loop diuretics (1.8%) and 1 patient ≥ 65 years of age (0.4%) treated with placebo (see sections 3.6 and 5.2).

Additionally, in the subgroup of patients with moderate renal impairment with eGFR ≥ 45 to < 60 mL/min/1.73m2, the proportion of patients with events related to volume depletion was higher in patients treated with FORXIGA 10 mg (4.7%) and FORXIGA 5 mg (2.3%) than in those treated with placebo (1.4%).

**Genital Infections**
Events of genital infections were reported in 5.5% and 0.6% of patients who received FORXIGA 10 mg and placebo, respectively, in the 13-study short-term, placebo-controlled 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 reported more frequently 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 and in females, and balanitis and in males.

In 9 of the 13 studies in the placebo-controlled pool, long-term treatment data was available. For this short-term plus long-term placebo-controlled pool (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 156 patients treated with FORXIGA 10 mg who experienced an infection, 106 (67.9%) had only one and 17 (10.9%) had 3 or more. Of the 19 patients treated with placebo who experienced an infection, 17 (89.5%) had only one and none had 3 or more .

In the 13-study short-term, placebo-controlled pool, patients who had a history of recurrent genital infection were more likely to have an event of genital infection (33.3% of patients with history of infection treated with FORXIGA 10 mg and 9.5% of patients with history of

infection on placebo) during the study than those without a history of infection (5.2% on FORXIGA 10 mg and 0.5% on placebo).

Overall, treatment with FORXIGA 5 mg was similar to treatment with FORXIGA 10 mg treatment.

**Urinary Tract Infections**

Events of urinary tract infections were reported in 4.7% and 3.5% of patients who received FORXIGA 10 mg and placebo, respectively, in the 13-study short-term, placebo-controlled pool. 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). 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 5.3).

In 9 of the 13 studies in the placebo-controlled pool, long-term treatment data was available. For 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 urinary tract infections were 8.6% (174/2026) in the FORXIGA 10 mg group and 6.2% (121/1956) in the placebo group.Of the 174 patients treated with FORXIGA 10 mg who experienced an infection, 135 (77.6%) had only one and 11 (6.3%) had 3 or more. Of the 121 patients treated with placebo who experienced an infection, 94 (77.7%) had only one and 12 (9.9%) had 3 or more.

In the 13-study short-term placebo-controlled pool, long term patients who had a history of recurrent urinary tract infection were more likely to have an event of urinary tract infection (6.0% of patients with history of infection treated with FORXIGA 10 mg and 5.9% of patients with history of infection on placebo) during the study than those without a history of infection (4.4% on FORXIGA 10 mg and 3.0% on placebo).

Overall, treatment with FORXIGA 5 mg was similar to treatment with FORXIGA 10 mg treatment.

**Hypoglycemia**

The frequency of hypoglycemia depended on the type of background therapy used in each study. Studies of FORXIGA as an add-on to sulfonylurea or as an add-on to insulin therapy had higher rates of hypoglycemia with FORXIGA treatment than with placebo treatment (see section 5.3).

In studies with FORXIGA used as monotherapy, add-on to metformin, add-on to pioglitazone, and initial combination with metformin for up to 102 weeks, there were no major episodes of hypoglycemia reported. In a study of FORXIGA 10 mg added on to sitagliptin (with or without metformin) for up to 48 weeks, one major episode of hypoglycemia was reported in a patient treated with FORXIGA 10 mg plus sitagliptin (without metformin). In these studies, the frequency of minor episodes of hypoglycemia 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 FORXIGA, there was one episode of major hypoglycemia reported in a patient treated with dapagliflozin 2.5 mg plus glimepiride. Minor episodes of hypoglycemia

were reported in 7.9% of patients treated with FORXIGA 10 mg plus glimepiride and 1% of patients treated with placebo plus glimepiride.

In an add-on to metformin study that compared FORXIGA to glipizide up to 104 weeks, there were 3 episodes (0.7%) of major hypoglycemia in patients treated with glipizide plus metformin and none in patients treated with FORXIGA plus metformin. Minor episodes of hypoglycemia were reported in 2.5% of patients treated with FORXIGA plus metformin and 42.4% of patients treated with glipizide plus metformin.

In an add-on to insulin study (with or without 2 additional oral anti-diabetic agents including metformin) that compared FORXIGA 10 mg plus insulin to placebo plus insulin up to 24 weeks, there was 1 (0.5%) episode of major hypoglycemia in a patient treated with FORXIGA 10 mg plus insulin and 1 (0.5%) episode in a patient treated with placebo plus insulin. At Week 104, major episodes of hypoglycemia were reported in 1.0% and 0.5% of patients treated with FORXIGA 10 mg or placebo added on to insulin, respectively.

Minor episodes were reported in 40.3% of patients treated with FORXIGA 10 mg plus insulin and in 34% of patients treated with placebo plus insulin for up to 24 weeks. At Week 104, minor episodes were reported in 53.1% and 41.6% of patients treated with FORXIGA 10 mg or placebo added on to insulin, respectively.114 In two additional studies that also included a large proportion of patients who received insulin as background therapy (alone or with one or more oral antidiabetic treatments) (see section 10.3), the rate of minor episodes of hypoglycemia was also increased in patients treated with FORXIGA 10 mg compared with those treated with placebo.

**Malignancies**

In the 21-study active- and placebo-controlled pool, the overall proportion of patients with malignant or unspecified tumors 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 section 11.1). When considering the cases of tumors occurring in the different organ systems, the relative risk associated with FORXIGA was above 1 for some tumors (eg, bladder and breast) and below 1 for others (eg, blood and lymphatic, ovary, renal tract).
Neither the increases nor decreases in risk were statistically significant in any of the organ systems. Considering the lack of tumor findings in nonclinical studies as well as the short latency between first drug exposure and tumor diagnosis, a causal relationship to any specific tumor type is considered unlikely.

**Liver Function Tests**

In the 21-study active- and placebo-controlled pool,there was no imbalance across treatment groups in the incidence of elevations of serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST), Alanine aminotransferase ALT >3 x ULN was reported in 1.2% of patients treated with FORXIGA 10 mg and 1.6% treated with comparator. Alanine aminotransferase (ALT) or AST >3 x ULN and bilirubin >2 x ULN was reported in 7 patients (0.1%) on any dose of FORXIGA, 5 patients (0.2%) on FORXIGA 10 mg, and 4 patients (0.1%) on comparator. One patient receiving FORXIGA experienced a liver adverse event with diagnoses of drug-induced hepatitis and/or autoimmune hepatitis.

**Cardiovascular Safety**
A meta-analysis of cardiovascular events across 21 active- and placebo-controlled studies was performed. Cardiovascular events were adjudicated by an independent adjudication committee.

The primary endpoint was the time to first event of the following: cardiovascular death, stroke, myocardial infarction, and hospitalization for unstable angina. Primary events occurred at a rate of 1.46% per 100 patient-years in patients treated with FORXIGA and 2.14% in comparator-treated patients, per 100 patient-years. The hazard ratio comparing FORXIGA to comparator was 0.79 (95% confidence interval; 0.58, 1.10). Treatment with FORXIGA is not associated with an increase in cardiovascular risk in patients with type 2 diabetes mellitus.

## 7.2 Postmarketing Experience

Not applicable.

## 7.3 Vital Signs

In the pool of 13 placebo-controlled studies, a decrease in blood pressure was observed in patients treated with FORXIGA 10 mg (mean seated systolic blood pressure change from baseline at Week 24 of -3.7 mmHg and mean seated diastolic blood pressure change of -1.8 mmHg for FORXIGA 10 mg vs −0.5 mmHg systolic and −0.5 mmHg diastolic blood pressure change for placebo group). Postural blood pressure measurement revealed orthostatic hypotension in 13.1% patients treated with FORXIGA-10-mg versus 11.3% of patients treated with placebo over the 24-week treatment period. In addition, in 2 studies with patients with type 2 diabetes and hypertension, postural blood pressure measurement revealed orthostatic hypotension in 3.2% of FORXIGA 10-mg-treated patients versus 1.7% of placebo-treated patients across the 2 studies over the 12-week treatment period (see section 10.3)

No other clinically meaningful changes in vital signs have been observed in patients treated with FORXIGA.

## 7.4 Laboratory Findings

**Hematocrit**

In the pool of 13 placebo-controlled studies, increases from baseline in mean hematocrit values were observed in FORXIGA-treated patients starting at Week 1 and continuing up to Week 16, when the maximum mean difference from baseline was observed. At Week 24, the mean changes frombaseline in hematocrit were 2.30% in the FORXIGA 10 mg group versus −0.33% in the placebo group. At Week 102, the mean changes were 2.68% versus −0.46%, respectively. By Week 24, hematocrit values >55% were reported in 1.3% of FORXIGA-10-mg–treated patients versus 0.4% of placebo-treated patients.Results were similar during the short-term plus longterm phase (the majority of patients were exposed to treatment for more than one year).

## Serum Inorganic Phosphorus

In the pool of 13 placebo-controlled studies, increases from baseline in mean serum phosphorus levels were reported at Week 24 in FORXIGA-10-mg–treated patients compared with placebo-treated patients (mean increases of 0.13 mg/Dl vs 0.04 mg/dL, respectively).Similar results were seen at Week 102. Higher proportions of patients with marked laboratory abnormalities of hyperphosphatemia (≥5.6 mg/dL if age 17-65 or ≥5.1 mg/dL if age ≥66) were reported in FORXIGA 10 mg group versus placebo at Week 24 (1.7% vs 0.9%, respectively) and during the short-term plus long-term phase (3.0% vs 1.6%, respectively). The clinical relevance of these findings is unknown.

### Lipids

In the pool of 13 placebo-controlled studies, small changes from baseline in mean lipid values were reported at Week 24 in FORXIGA- 10-mg–treated patients compared with placebo-treated patients. Mean percent change from baseline at Week 24 for FORXIGA 10 mg versus placebo, respectively, was as follows: total cholesterol, 2.5% versus 0.0%; HDL cholesterol, 6.0% versus 2.7%; LDL cholesterol, 2.9% versus −1.0%; triglycerides, −2.7% versus -0.7%. Mean percent change from baseline at Week 102 for FORXIGA 10 mg versus placebo, respectively, was as follows: total cholesterol, 2.1% versus −1.5%; HDL cholesterol, 6.6% versus 2.1%; LDL cholesterol, 2.9% versus −2.2%; triglycerides, −1.8% versus -1.8%. The ratio between LDL cholesterol and HDL cholesterol decreased for both treatment groups at Week 24.

## 8 OVERDOSE

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 for patients treated with dapagliflozin was similar to placebo. In clinical studies where once-daily doses of up to 100 mg (10 times the MRHD) of dapagliflozin were administered for 2 weeks in healthy subjects and type 2 diabetes patients, the incidence of hypoglycemia for subjects administered dapagliflozin was slightly higher than placebo and was not dose related. Rates of adverse events including dehydration or hypotension hypoglycemia for patients treated with dapagliflozin 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 hemodialysis has not been studied.

## 9 PHARMACOLOGICAL PROPERTIES

### 9.1 Pharmacodynamics

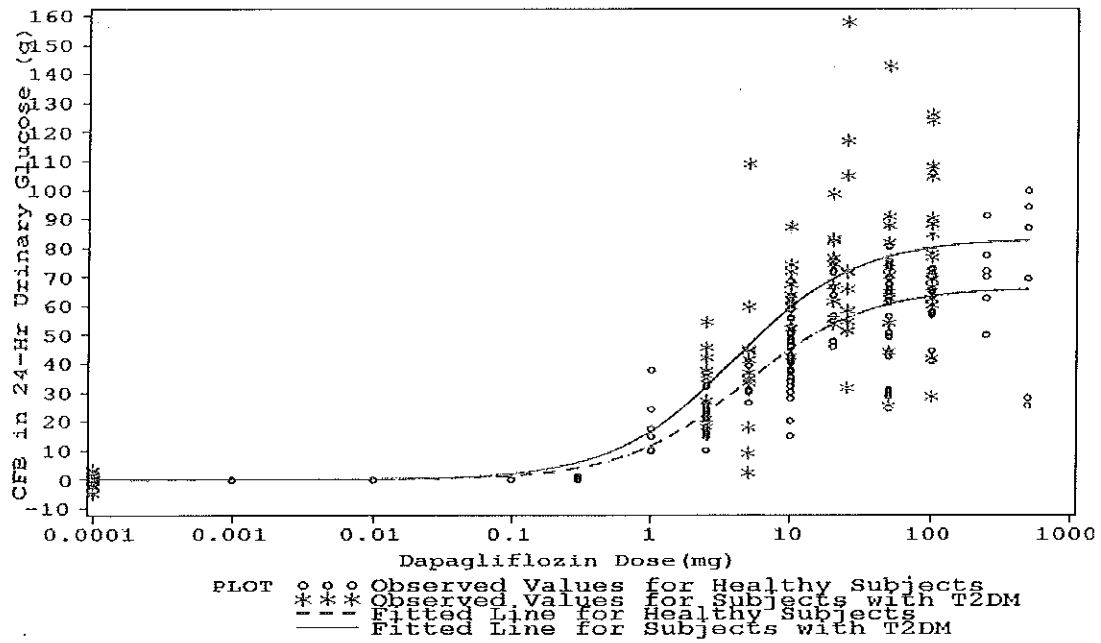
### General

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

This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases inurinary 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 0.33 mg/dL to 0.87 mg/dL.

**Figure 1 Scatter Plot and Fitted Line of Change from Baseline in 24-hour Urinary Glucose Amount versus Dapagliflozin Dose in Healthy Subjects and Subjects with 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.

## 9.2 Mechanism of Action

Dapagliflozin is a highly potent, selective, and reversible inhibitor of sodium glucose cotransporter 2 (SGLT2) that improves glycemic control in patients with type 2 diabetes mellitus by reducing renal glucose reabsorption leading to urinary excretion of excess glucose (glucuresis). 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 reduces maximum tubular glucose transport by 55% and reduces renal glucose reabsorption such that glucose appears in the urine at normal plasma glucose levels.151 Thus, dapagliflozin improves both fasting and postprandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary excretion of excess glucose. 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 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 weight reduction is 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. Inhibition of glucose and sodium cotransport by dapagliflozin is also associated with mild diuresis and transient natriuresis.

Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is greater than 1400 times more selective for SGLT2 versus SGLT1, the major transporter in the gut responsible for glucose absorption.

## 9.3 Pharmacokinetics

## Absorption

Dapagliflozin is rapidly and well absorbed after oral administration and can be administered with or without food.Maximum dapagliflozin plasma concentrations ($C_{max}$) are usually attained within 2 hours after administration in the fasted state. The $C_{max}$ and AUC values increase proportionally to the increment in dapagliflozin dose. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Food has relatively modest effects on the pharmacokinetics of dapagliflozin in healthy subjects.Administration with a high-fat meal decreases dapagliflozin $C_{max}$ by up to 50% and prolonged $T_{max}$ by approximately 1 hour, but does 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 is not altered in various disease states (eg, renal or hepatic impairment).

**Metabolism**

Dapagliflozin is a C-linked glucoside, meaning the aglycone component is attached to glucose by a carbon-carbon bond, thereby conferring stability against glucosidase enzymes. The mean plasma terminal half-life (t 1/2) for dapagliflozin is 12.9 hours161 following a single oral dose of FORXIGA 10 mg to healthy subjects. Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-Oglucuronide accounted for 61% of a 50 mg [14C]-dapagliflozin dose and is the predominant drug-related component in human plasma, accounting for 42% (based on AUC [0-12 hour]) of total plasma radioactivity, similar to the 39% contribution by parent drug. Based on AUC, no other metabolite accounts for >5% of the total plasma radioactivity. Dapagliflozin 3-Oglucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP-mediated metabolism is 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 administration of 50 mg [14C]-dapagliflozin dose, 96% is recovered; 75% in urine and 21% in feces. In feces,approximately 15% of the dose is excreted as parent drug.

**Special Populations**
No dosage adjustments based on pharmacokinetic analyses are recommended for mild to moderate renal impairment; mild, moderate, and severe hepatic impairment; age; gender; race; and body weight.

**Renal Impairment**
FORXIGA should not be used in patients with moderate or severe renal impairment (eGFR persistently <45 mL/min/1.73m2 or CrCl persistently <60 mL/min) (see sections 3.2 and 5.1). At steady-state (20 mgonce-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 were lower in patients with moderate or severe renal impairment as compared to patients with normal and mild renal impairment. The steady-state 24-hour urinary glucose excretion was highly dependent on renal function, and 85, 52, 18, and 11 g of glucose/day was excreted by patients with type 2 diabetes mellitus and normal renal function or mild, moderate, or severe renal impairment, respectively. There were no differences in the protein binding of dapagliflozin between renal impairment groups or compared to healthy subjects. The impact of hemodialysis on dapagliflozin exposure is not known.

**Hepatic Impairment**
For dosing recommendations for patients with moderate or severe hepatic impairment see section 3.3. 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 patients with hepatic impairment compared to healthy subjects. In patients with mild or moderate hepatic impairment, mean $C_{max}$ and AUC of dapagliflozin were up to 12% and 36% higher, respectively, compared to healthy matched

control subjects. These differences were not considered to be clinically meaningful. 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. No dose adjustment is required for patients with severe hepatic impairment. However, the benefit- risk for the use of dapagliflozin in patients with severe hepatic impairment should be individually assessed since the safety and efficacy of dapagliflozin have not been specifically studied in this population.

Age

No dosage adjustment for dapagliflozin from the dose of 10 mg once daily is recommended on the basis of age. The effect of age (young: ≥18 to <40 years [n=105] and elderly: ≥65 years [n=224]) was evaluated as a covariate in a population pharmacokinetic model and compared to patients ≥40 to <65 years using data from healthy subject and patient studies). The mean dapagliflozin systemic exposure (AUC) in young patients was estimated to be 10.4% lower than in the reference group (90% CI; 87.9, 92.2%) and 25% higher in elderly patients compared to the reference group (90% CI; 123, 129%). These differences in systemic exposure were considered to not be clinically meaningful.

**Pediatric and Adolescent**

Pharmacokinetics in the pediatric 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.168 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, or Asian) was evaluated as a covariate in a population pharmacokinetic model using data from healthy subject and patient studies.168 Differences in systemic exposures between these races were small. Compared to Whites (n=1147), Asian subjects (n=47) had no difference in estimated mean dapagliflozin systemic exposures (90% CI range; 3.7% lower, 1% higher). Compared to Whites, Black subjects (n=43) had 4.9% lower estimated mean dapagliflozin systemic exposures (90% CI range; 7.7% lower, 3.7% lower).

**Body Weight**

No dose adjustments from the proposed dapagliflozin dose of 10 mg once daily 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.168 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 early phase 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.

## 10 CLINICAL TRIAL INFORMATION

FORXIGA has been studied as monotherapy and in combination with metformin, pioglitazone, glimepiride, sitagliptin, or insulin. FORXIGA has also been studied in patients with type 2 diabetes and cardiovascular disease and those with type 2 diabetes and hypertension A total of 9412 patients with type 2 diabetes mellitus were treated in 16 double-blind, controlled clinical studies conducted to evaluate the safety and efficacy of FORXIGA; 5952 patients in these studies were treated with FORXIGA. Thirteen studies had a treatment period of 24 weeks two of 12 weeks, and one study was 52 weeks. Of the 16, , 11 studies had longterm extensions ranging from 24 to 80 weeks (up to total study duration of 104 weeks). Across the 16 clinical studies, the mean age was 57 years (range, 18 to -92 years), and the mean duration of diabetes was 8 years (range, <1 to 54 years). Fifty-five percent (55%) of patients were men, 82% were White, 10% were Asian, and 4% were Black,. Eighty-one percent (81%) of patients had a BMI of $\geq$27 kg/m$^2$. FORXIGA has also been studied in patients with mild (53% of the population studied) to moderate (12% of the population studied) renal impairment.

Treatment with FORXIGA as monotherapy and in combination with metformin, glimepiride, pioglitazone, sitagliptin, or insulin produced clinically relevant and statistically significant reductions 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 104 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 were seen with FORXIGA combination treatments compared to control. Body-weight reductions were sustained in long-term extensions up to 104 weeks. In a dedicated clinical study, decrease in weight was mainly attributable to a reduction in body-fat mass as measured by DXA. In two studies of FORXIGA 10 mg in type 2 diabetes patients with cardiovascular disease, statistically significant improvements in HbA1c and significant reductions in body weight and seated systolic blood pressure were seen at Week 24 in patients treated with FORXIGA 10 mg compared to those treated with placebo, and were sustained through Week 104. In two studies of FORXIGA 10 mg in type 2 diabetes patients with hypertension, statistically significant reductions in mean seated systolic blood pressure were also seen in patients treated with FORXIGA 10 mg combined with other oral antidiabetic and antihypertensive treatments (an ACE or ARB in one study and an ACE or ARB plus one additional antihypertensive treatment in another study) compared to those treated with placebo at Week 12

FORXIGA was evaluated at 10 mg once daily in 14 of 16 double-blind studies. Doses of dapagliflozin 2.5 mg and FORXIGA 5 mg were also evaluated in some of these studies; 2.5 mg was not consistently effective for glycemic control, and 10 mg had numerically better numerical efficacy and comparable safety to FORXIGA 5 mg.

AstraZeneca

## 10.1 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 one monotherapy study, a total of 558 treatment-naive 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 ≥7% and ≤10% were randomized to dapagliflozin 2.5 mg, FORXIGA 5 mg, or 10 mg once daily in either the morning (QAM, main cohort) or evening (QPM), or placebo in the morning only.

At Week 24, treatment with FORXIGA 10 mg QAM provided significant improvements in HbA1c and FPG compared with placebo (Table 2, Figure 2). Overall, the PM administration of FORXIGA had a comparable safety and efficacy profile to FORXIGA administered in the AM. Adjusted mean change from baseline in HbA1c and FPG was −0.61% and −27.0 mg/dL, respectively, at Week 102 in the QAM group for patients treated with FORXIGA 10 mg, and −0.18% and −5.3 mg/dL, 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 for placebo (12.0%) than for FORXIGA 10 mg (0.0%). By Week 102 (adjusted for baseline HbA1c), more patients treated with placebo (44.0%) required rescue therapy than patients treated with FORXIGA 10 mg (35.0%).

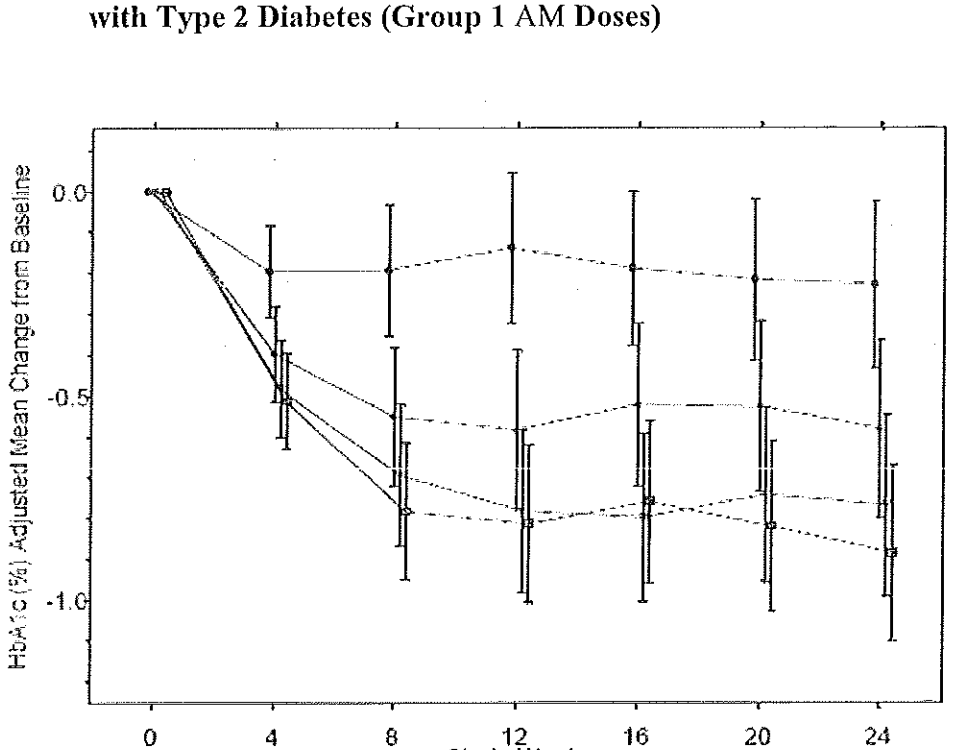
**Table 2: Results at week 24 (LOCF[*]) in a placebo – controlled study of FORXIGA Monotherapy in patients with Type 2 Diabetes (Main Cohort AM Doses)**

| Efficacy Parameter | FORXIGA 10mg 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 (mg/dL)** | | |
| Baseline (mean) | 166.6 | 159.9 |
| Change from baseline (adjusted mean[‡]) | −28.8 | −4.1 |
| Difference from placebo (adjusted mean[‡]) | −24.7[§] | |

| | | |
|---|---|---|
| (95% CI) | (−35.7, −13.6) | |
| **Body Weight (kg)** | | |
| Baseline (mean) | 94.13 | 88.77 |
| Change from baseline (adjusted mean‡) | −3.16 | −2.19 |
| Difference from placebo (adjusted mean‡) | −0.97 | |
| (95% CI) | (−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 versus placebo.
¶ Not evaluated for statistical significance as a result of the sequential testing procedure for the secondary endpoints.

**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

Another 24-week study conducted evaluating dapagliflozin 1 mg, 2.5 mg and FORXIGA 5 mg monotherapy versus placebo also showed clinically relevant and statistically significant improvements in glycemic parameters and body weight.

## 10.2 Combination Therapy

FORXIGA was studied as add-on to metformin, add-on to sulfonylurea (glimepiride), add-on to thiazolidinedione (pioglitazone), add-on to DPP4 inhibitor (sitagliptin), and add-on to insulin (with or without other antidiabetic therapies).

### 10.2.1 Add-On 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 versus sulfonylurea added to metformin.

**Initial Combination Therapy with Metformin**

A total of 1241 treatment-naive patients with inadequately controlled type 2 diabetes (HbA1c ≥7.5% and ≤12%) participated in two active-controlled studies of 24-weeks duration to evaluate the efficacy and safety of initial therapy with FORXIGA 5 mg or 10 mg in combination with metformin extended-release formulation (XR).in One study, 638 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 XR dose was up-titrated weekly in 500 mg increments, as tolerated, with a median dose achieved of 2000 mg.

The combination treatment of FORXIGA 10 mg plus metformin XR provided significant improvements in HbA1c and FPG compared with either of the monotherapy treatments and significant reductions in body weight compared with metformin XR alone. (Table 4, Figures 3 and 3).FORXIGA 10 mg as monotherapy also provided significant improvements in FPG and significant reduction in body weight compared with metformin XR alone and was noninferior to metformin XR 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 for treatment with metformin XR plus placebo (13.5%) than on FORXIGA 10 mg plus placebo and FORXIGA 10 mg plus metformin XR (7.8% and 1.4%, respectively).

**Table 3: Results at week 24 (LOCF*) in an Active– controlled study of FORXIGA Initial Combination Therapy with Metformin XR**

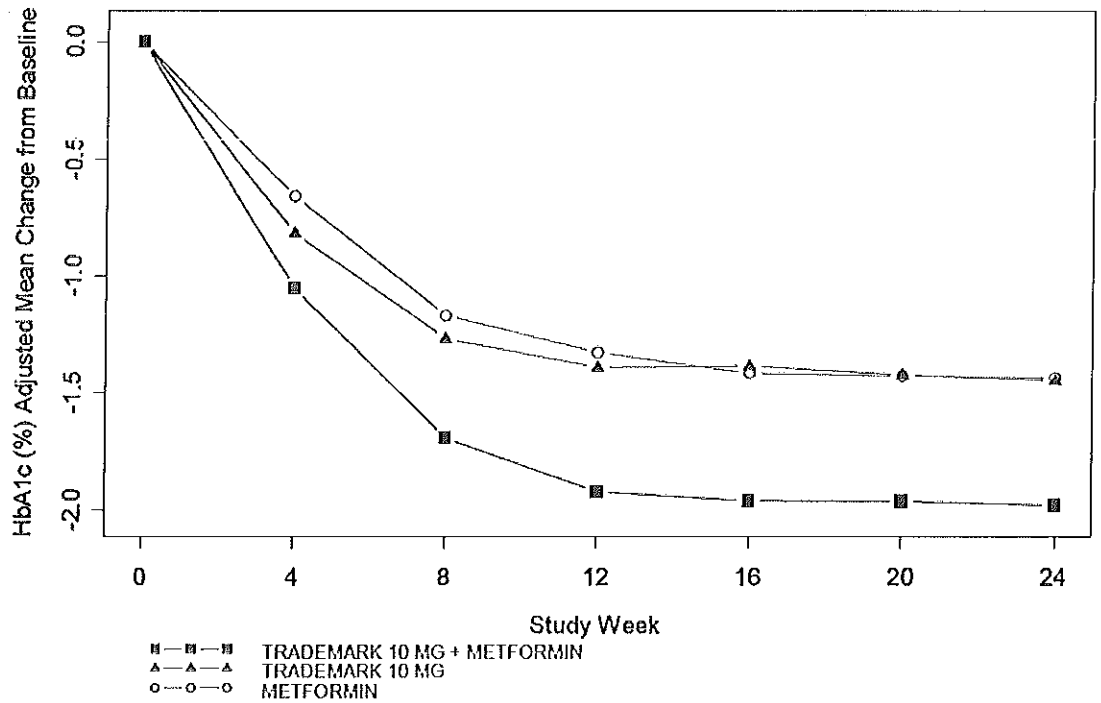
| Efficacy Parameter | FORXIGA 10 mg + Metformin XR N=211[†] | FORXIGA 10mg N=219[†] | Metformin XR N=208[†] |
|---|---|---|---|
| **HbA1c (%)** | | | |
| Baseline (mean) | 9.10 | 9.03 | 9.03 |
| Change from baseline (adjusted mean[‡]) | −1.98 | −1.45 | −1.44 |
| Difference from FORXIGA (adjusted mean[‡]) (95% CI) | −0.53[§] (−0.74,−0.32) | | |
| Difference from metformin XR (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¶ | | |
| **FPG (mg/dL)** | | | |
| Baseline (mean) | 189.6 | 197.5 | 189.9 |
| Change from baseline (adjusted mean‡) | −60.4 | −46.4 | −34.8 |
| Difference from FORXIGA (adjusted mean‡) (95% CI) | −13.9§ (−20.9, −7.0) | | |
| Difference from metformin XR (adjusted mean‡) (95% CI) | −25.5§ (−32.6, −18.5) | 11.6¶ (−18.6, −4.6) | |
| **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 XR (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 XR.
# p-value <0.05.

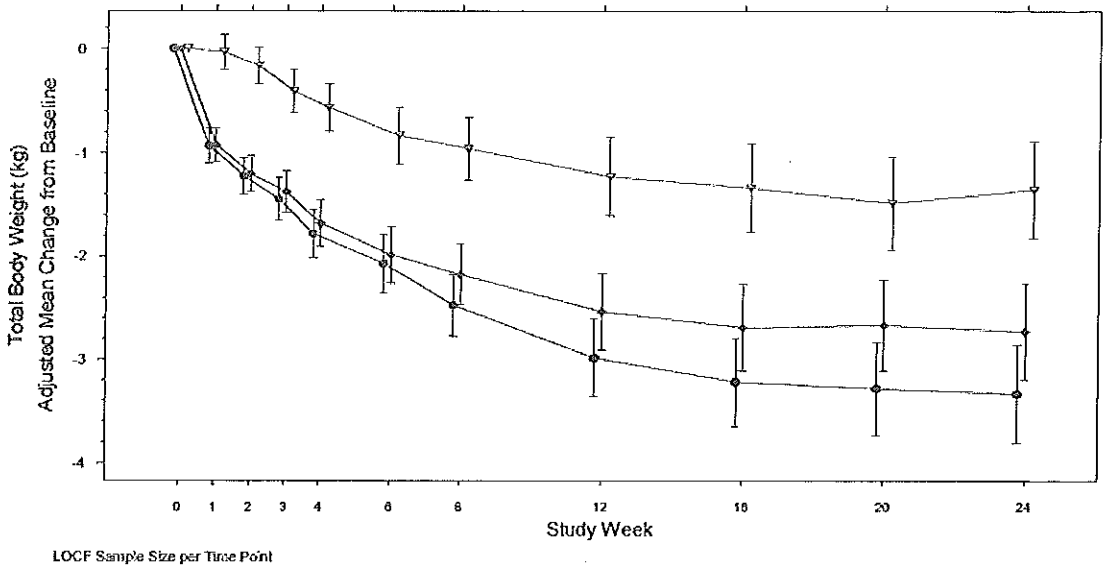
**Figure 3: Adjusted Mean Change from Baseline Over Time (LOCFa) in HbA1c in a 24-Week Active-Controlled Study of FORXIGA Initial Combination Therapy with Metformin XR**




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

AstraZeneca

**Figure 4: Adjusted Mean Change from Baseline Over Time (LOCFa) in Total Body Weight (kg) in a 24-Week Active-Controlled Study of Dapagliflozin 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

Another 24-week study evaluating FORXIGA 5 mg plus metformin XR showed clinically relevant and statistically significant improvements in glycemic parameters versus FORXIGA 5 mg monotherapy and metformin XR monotherapy

***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, FORXIGA 5 mg, or 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 and FPG, and significant reduction in body weight compared with placebo at Week 24 (Table 5). At Week 102, adjusted mean change from baseline in HbA1c (see Figure 5), FPG, and body weight was −0.78%, −24.5 mg/dL, and −2.81 kg , respectively, for patients treated with FORXIGA 10 mg plus metformin and 0.02%, −10.4 mg/dL, and −0.67 kg for patients treated with placebo plus metformin based on the longitudinal repeated measures analysis excluding data after rescue (Figure 5). 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 (adjusted analysis) more patients treated with placebo plus metformin (60.1%) required rescue therapy than patients treated with FORXIGA 10 mg plus metformin (44.0%).

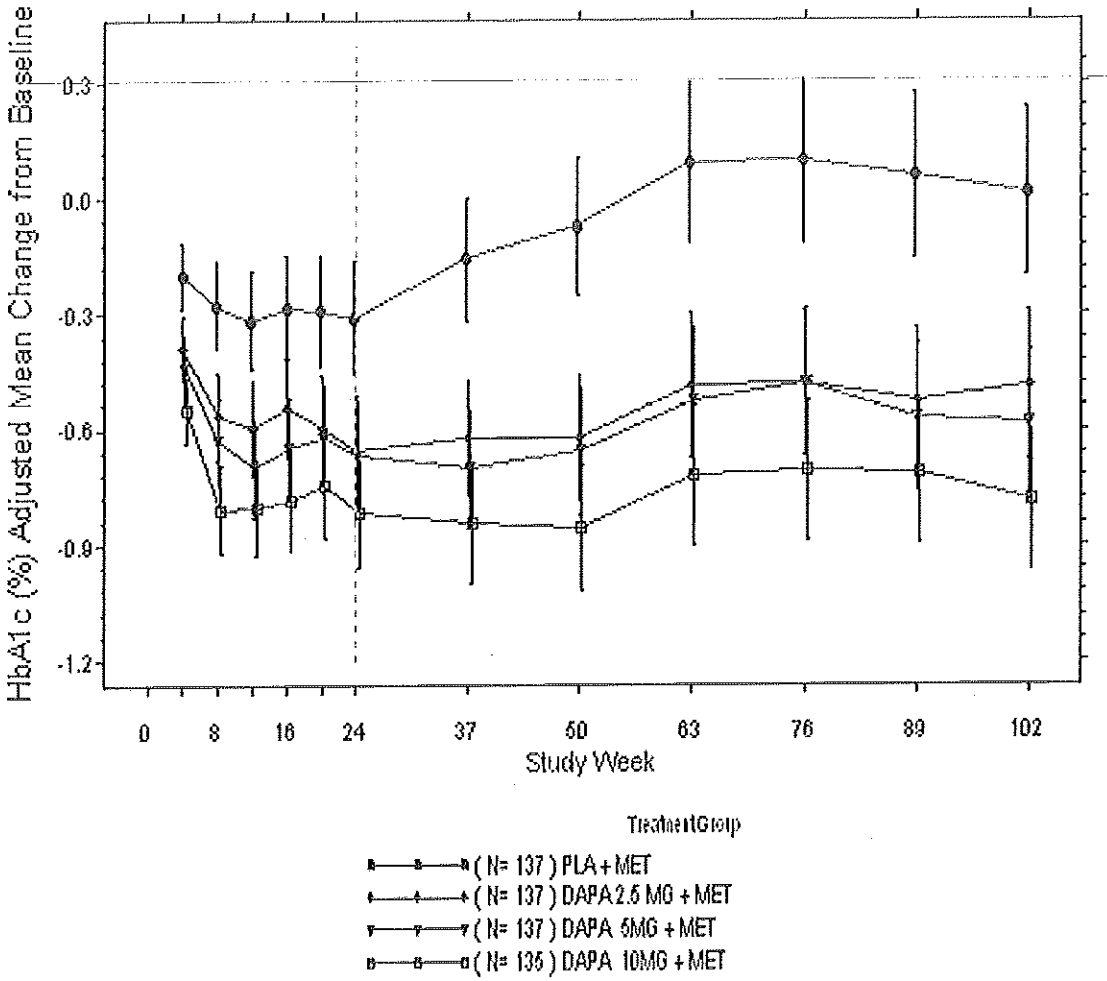
**Table 4: Results at week 24 (LOCF*) Placebo– controlled study of FORXIGA in Add- on Combination with Metformin**

| 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 (mg/dL)** | | |
| Baseline (mean) | 156.0 | 165.6 |
| Change from baseline at week 24 (adjusted mean‡) | −23.5 | −6.0 |
| Difference from Placebo (adjusted mean‡) (95% CI) | −17.5§ (−25.0, −10.0) | |
| Change from Baseline at week 1 (adjusted mean‡) | −16.5§ (N=115) | 1.2 (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 versus placebo + metformin.
¶ p-value <0.05 versus 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)**




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

**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 a 52-week, glipizide-controlled, non-inferiority study with a 156- week extension period to evaluate FORXIGA as add-on therapy to metformin.5 Patients on metformin at a dose of at least 1500 mg per day were randomized following a 2-week placebo lead-in period to glipizide or dapagliflozin (5 mg or 2.5 mg, respectively) and were up-titrated over 18 weeks to optimal glycemic effect (FPG <110 mg/dL, <6.1 mmol/L) or to the highest dose level (up to glipizide 20 mg and FORXIGA 10 mg) as tolerated by patients. Thereafter, doses were kept constant, except for down-titration to prevent hypoglycemia.

At the end of the titration period, 87% of patients treated with FORXIGA had been titrated to the maximum study dose (10 mg) versus 73% treated with glipizide (20 mg).FORXIGA led to a similar mean reduction in HbA1c from baseline at Week 52,compared with glipizide, thus demonstrating non-inferiority (Table 5). FORXIGA treatment led to a significant mean reduction in body weight from baseline at Week 52 compared with a mean increase in body weight in the glipizide group.

At Week 104, adjusted mean change from baseline in HbA1c and body weight was −0.32% and −3.70 kg, respectively, for patients treated with FORXIGA and −0.14% and 1.36 kg for

patients treated with glipizide based on the longitudinal repeated measures analysis (Figures 6 and 7). The percent of patients achieving weight loss of ≥5% (adjusted) was 23.8% for patients treated with FORXIGA and 2.8% for patients treated with glipizide. By Weeks 52 and 104, the proportion of patients who discontinued for lack of glycemic control (adjusted for baseline HbA1c) was higher for glipizide plus metformin (3.6% and 21.6%, respectively) than for FORXIGA plus metformin (0.2% and 14.5%, respectively).

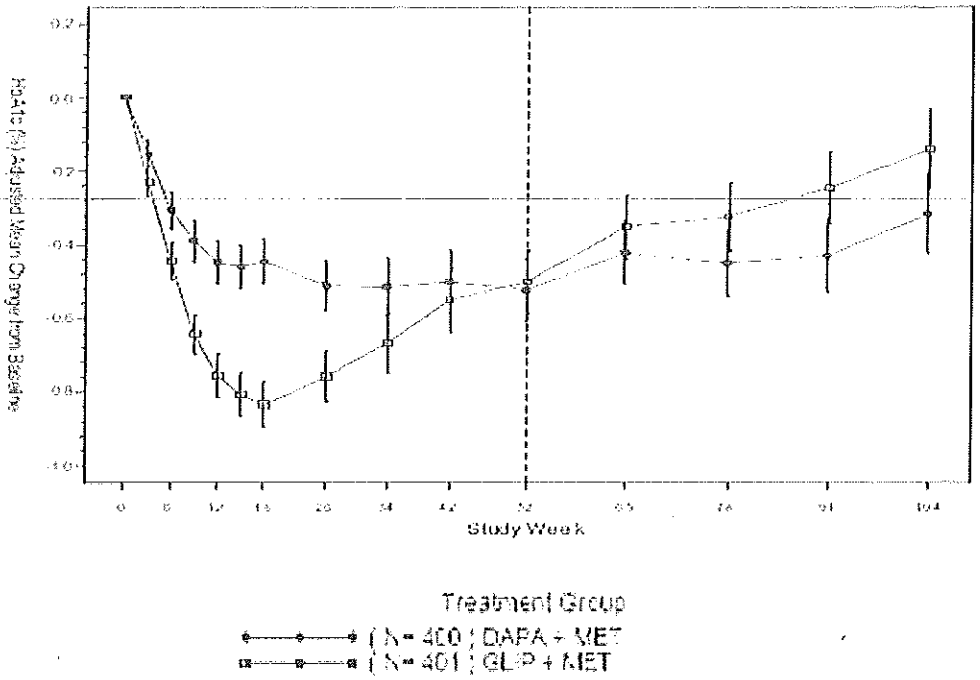
Rescue for lack of glycemic control was not available in this study. At 52 and 104 weeks, respectively, a significantly lower proportion of patients treated with FORXIGA (3.5% and 4.3%) experienced at least one event of hypoglycemia, compared to glipizide (40.8% and 47.0%,)

**Table 5: 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[‡]) (95% CI) | −0.00[§] (−0.11, −0.11) | |
| **Body Weight (kg)** | | |
| Baseline (mean) | 88.44 | 87.60 |
| Change from baseline (adjusted mean[‡]) | −3.22 | 1.44 |
| Difference from Glipizide +Metformin (adjusted mean[‡]) (95% CI) | −4.65[§] (−5.14, −4.17) | |
| Percent of patients achieving weight loss >5% (adjusted) (95%CI) | 33.3%[¶] (28.7, 37.9) | 2.5% (1.0, 4.0) |

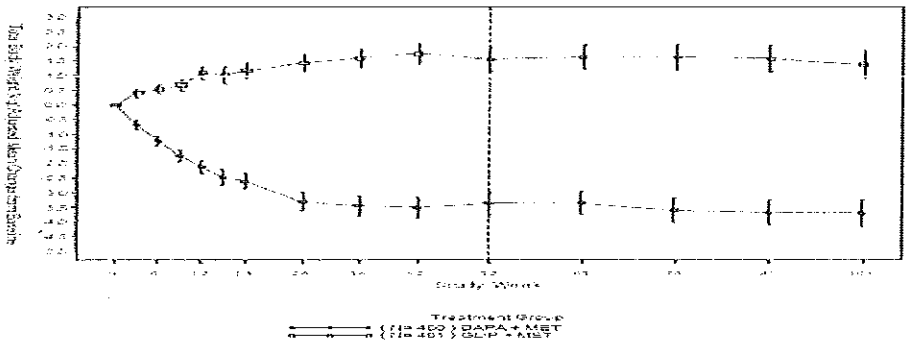
* LOCF: last observation carried forward.
[†] Randomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.
[‡] Least squares mean adjusted for baseline value.
[§] Non-inferior to glipizide + metformin.
[¶] p-value <0.0001.

**Figure 6: Adjusted Mean Change from Baseline Over Time in HbA1c (%) in a 104-Week Active-Controlled Study Comparing FORXIGA to Glipizide as Add-on to Metformin (Longitudinal Repeated Measures Analysis, Excluding Data after Rescue)**




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 in a 104-Week Active-Controlled Study Comparing FORXIGA to Glipizide as Add-on to Metformin (Longitudinal Repeated Measures Analysis, Excluding Data after Rescue)**



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

## 10.2.2 Add-On Combination with Other Antidiabetic 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 extensionperiod to evaluate FORXIGA in combination with glimepiride (a sulfonylurea).

Patients on at least half the maximum recommended dose of a glimepiride as monotherapy (4 mg) for at least 8 weeks lead-in were randomized to dapagliflozin 2.5 mg, FORXIGA 5 mg, or 10 mg, or placebo in addition to glimepiride 4 mg per day. Down-titration of glimepiride to 2 mg or 0 mg was allowed for hypoglycemia during the treatment period; no uptitration of glimepiride was allowed.

In combination with glimepiride, treatment with FORXIGA 10 mg provided significant improvement in HbA1c, FPG, 2-hour PPG, and significant reduction in body weight compared with placebo plus glimepiride at Week 24 (Table 7, Figure 8). At Week 48, adjusted mean change from baseline in HbA1c,FPG, and body weight were −0.73%, −28.8 mg/dL, and −2.41 kg, respectively, for patients treated with FORXIGA 10 mg plus glimepiride, and −0.04%, 2.6 mg/dL, 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

At Week 24,the proportion of patients who were rescued or discontinued for lack of glycemic control (adjusted for baseline HbA1c) was higher for placebo plus glimepiride (16.2%) than for FORXIGA 10 mg plus glimepiride (2.0%). By Week 48 (adjusted for baseline HbA1c) more patients on placebo plus glimepiride (52.1%) required rescue therapy than patients on FORXIGA 10 mg plus glimepiride (18.4%).

**Add-on Combination Therapy with a Thiazolidinedione**

A total of 420 patients with type 2 diabetes with inadequate glycemic control (HbA1c ≥7% and ≤10.5 %) participated in a 24-week, placebo-controlled study with a 24-week extension period to evaluate FORXIGA in combination with pioglitazone (a thiazolidinedione) alone. Patients on a stable dose of pioglitazone of 45 mg/day (or 30 mg/day, if 45 mg/day was not tolerated) for 12 weeks were randomized after a 2-week lead-in period to 5 mg or 10 mg of FORXIGA or placebo in addition to their current dose of pioglitazone. Dose titration of FORXIGA or pioglitazone was not permitted during the study.

In combination with pioglitazone, treatment with FORXIGA 10 mg provided significant improvements in HbA1c, 2-hour PPG, FPG, the proportion of patients achieving HbA1c <7% and a significant reduction in body weight compared with the placebo plus pioglitazone treatment groups (Table 6, Figure 9) at Week 24. Treatment with FORXIGA 10 mg plus pioglitazone also led to a significant reduction in waist circumference compared with the placebo plus pioglitazone group. At Week 48, adjusted mean change from baseline in HbA1c, FPG, and body weight were −1.21%, −33.1 mg/dL, and 0.69 kg, respectively, for patients treated with FORXIGA 10 mg plus pioglitazone, and −0.54%, −13.1 mg/dL, and 2.99 kg for patients treated with placebo 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 in the placebo plus pioglitazone group (11.6%) than in the FORXIGA 10 mg plus pioglitazone group (3.7%) at Week 24. By Week 48 (adjusted from baseline), more patients treated with placebo plus pioglitazone (33.8%) required rescue therapy than patients treated with FORXIGA 10 mg plus pioglitazone (11.8%).

**Add-on Combination Therapy with Insulin**

A total of 808 patients with type 2 diabetes who had inadequate glycemic control (HbA1c ≥7.5% and ≤10.5%) were randomized in a 24-week, placebo-controlled study with an 80-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, FORXIGA 5 mg, or 10 mg, or placebo in addition to their current dose of insulin and other OADs, if applicable. Patients were stratified according to the presence or absence of background OADs. Up- or down-titration of insulin was only permitted during the treatment phase in patients who failed to meet specific glycemic goals. Dose modifications of blinded study medication or OADs

were not allowed during the treatment phase, with the exception of titration of OADs 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. At Week 24, FORXIGA 10 mg dose provided significant improvement in HbA1c, and mean insulin dose and a significant reduction in body weight compared with placebo in combination with insulin, with or without up to 2 OADs (Table 6); the effect of FORXIGA on HbA1c was similar in patients on insulin alone and patients on insulin plus OADs. At Week 48, adjusted mean change from baseline in HbA1c, FPG, and body weight was −0.93%, −21.5 mg/dL, and −1.79 kg, respectively, for patients treated with FORXIGA 10 mg plus insulin and −0.43%, −4.4 mg/dL, and −0.18 kg, respectively, for patients treated with placebo plus insulin based on the longitudinal repeated measures analysis excluding data after rescue.At Week 104, adjusted mean change from baseline in HbA1c, FPG, and body weight was −0.71%, −18.2 mg/dL, and −1.97 kg, respectively, for patients treated with FORXIGA 10 mg plus insulin, and −0.06%, −11.2 mg/dL, and 0.91 kg, respectively, for patients treated with placebo plus insulin based on the longitudinal repeated measures analysis excluding data after rescue (see Figure 10).

At Week 24, a significantly higher proportion of patients on FORXIGA 10 mg reduced their 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 for placebo plus insulin (29.2%) than for FORXIGA 10 mg plus insulin (9.7%). By Weeks 48 and 104, the insulin dose remained stable in patients treated with FORXIGA 10 mg at an average dose of 76 IU/day, but continued to increase (mean increase 10.5 IU and 18.3 IU, respectively, from baseline) in placebo-treated patients. By Weeks 48 and 104 (adjusted for baseline HbA1c) , more patients treated with placebo required up-titration with insulin to maintain glycemic levels or discontinued due to lack of glycemic control (42.8% and 50.4%, respectively) compared with patients treated with FORXIGA 10 mg (15.3% and 25.5%, respectively).

**Table 6: Results of 24 week (LOCF*) placebo –controlled studies of Forxiga in combination with Antidiabetic agents**

| Efficacy Parameter | Forxiga 10mg | Placebo |
|---|---|---|
| **In Combination with Sulfonylurea (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 (adjusted mean[‡]) (95% CI) | −0.68[§] (−086, −0.51) | |
| Percent of patients achieving HbA1c <7% adjusted for baseline | 31.7%[§] | 13.0% |
| **FPG (mg/dL)** | | |
| Baseline (mean) | 172.4 | 172.7 |
| Change from baseline (adjusted mean[‡]) | −28.5 | −2.0 |
| Difference from Placebo (adjusted mean[‡]) (95% CI) | −26.5[§] (−33.5, −19.5) | |
| **2-hour PPG[¶] (mg/dL)** | | |
| Baseline (mean) | 329.6 | 324.1 |

**Table 6: Results of 24 week (LOCF*) Placebo –controlled studies of**

| Efficacy Parameter | Forxiga 10mg | Placebo |
|---|---|---|
| Change from baseline (adjusted mean‡) | −60.6 | −11.5 |
| Difference from Placebo (adjusted mean‡) (95% CI) | −49.1§ (−64.1, −34.1) | |
| **Body Weight (kg)** | | |
| Baseline (mean) | 80.56 | 80.94 |
| Change from baseline (adjusted mean‡) | −2.26 | −0.72 |
| Difference from Placebo (adjusted mean‡) (95% CI) | −1.54§ (−2.17, −0.92) | |
| **In Combination with Thiazolidinedione (Pioglitazone)** | | |
| **Intent-to-Treat Population** | N=140# | N=139# |
| **HbA1c (%)** | | |
| Baseline (mean) | 8.37 | 8.34 |
| Change from baseline (adjusted mean‡) | −0.97 | −0.42 |
| Difference from placebo (adjusted mean‡) (95% CI) | −0.55§ (−0.78, −0.31) | |
| Percent of patients achieving HbA1c <7% adjusted for baseline | 38.8%** | 22.4% |
| **FPG (mg/dL)** | | |
| Baseline (mean) | 164.9 | 160.7 |
| Change from baseline (adjusted mean‡) | −29.6 | −5.5 |
| Difference from placebo (adjusted mean‡) (95% CI) | −24.1§ (−32.2, −16.1) | |
| **2-hour PPG† (mg/dL)** | | |
| Baseline (mean) | 308.0 | 293.6 |
| Change from baseline (adjusted mean‡) | −67.5 | −14.1 |
| Difference from placebo (adjusted mean‡) (95% CI) | 53.3§ (−71.1, −35.6) | |
| **Body Weight (kg)** | | |
| Baseline (mean) | 84.82 | 86.40 |
| Change from baseline (adjusted mean‡) | −0.14 | 1.64 |
| Difference from placebo (adjusted mean‡) (95% CI) | -1.78§ (−2.55, −1.02) | |

## Table 6: Results of 24 week (LOCF*) Placebo –controlled studies of Forxiga in combination with Antidiabetic agents

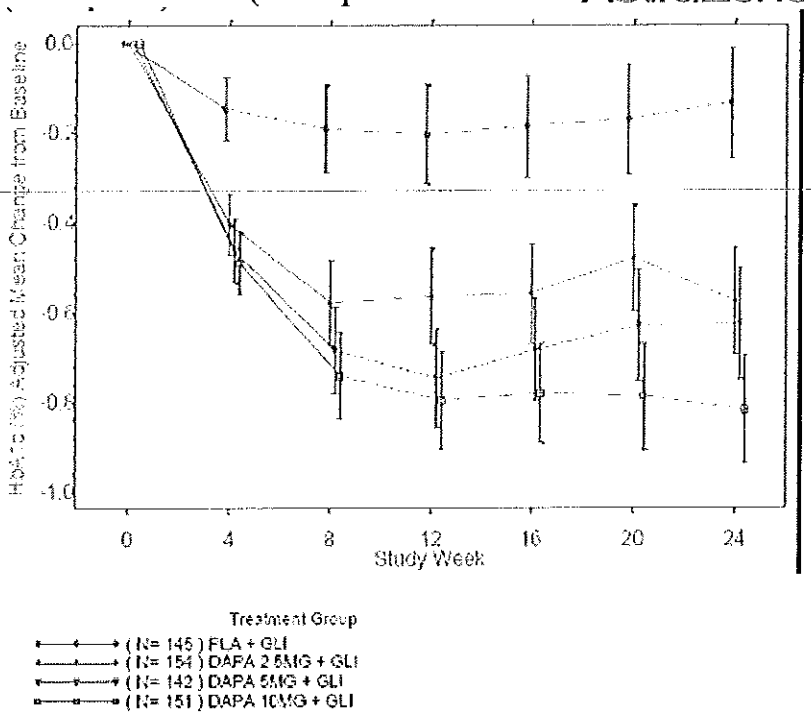
| Efficacy Parameter | Forxiga 10mg | Placebo |
|---|---|---|
| Change from baseline in waist circumference (cm) (adjusted mean‡) | −0.17** | 1.38 |
| **In Combination with Insulin with or without up to 2 Oral Antidiabetic Therapies** | | |
| **Intent-to-Treat Population** | N=194† | N=193† |
| **HbA1c (%)** | | |
| Baseline (mean) | 8.58 | 8.46 |
| Change from baseline (adjusted mean‡) | −0.90 | −0.30 |
| Difference from Placebo (adjusted mean‡) | 0.60§ | |

| | | |
|---|---|---|
| (95% CI) | (−0.74, −0 | |
| **Mean Daily Insulin Dose (IU)**[††] | | |
| Baseline (mean) | 77.96 | 73.96 |
| Change from baseline (adjusted mean[‡]) | −1.16 | 5.08 |
| Difference from placebo<br>(95% CI) | − 6.23[§]<br>(−8.84, −3.63) | |
| Percent of patients with mean daily insulin dose reduction of at least 10% adjusted for baseline | 19.6%** | 11.0% |
| **FPG (mg/dL)** | | |
| Baseline (mean) | 173.7 | 170.0 |
| Change from baseline (adjusted mean[‡]) | −21.7 | 3.3 |
| Difference from placebo (adjusted mean[‡])<br>(95% CI) | −25.0[§]<br>(−34.3, −15.8) | |
| **Body Weight (kg)** | | |
| Baseline (mean) | 94.63 | 94.21 |
| Change from baseline (adjusted mean[‡]) | −1.67 | 0.02 |
| Difference from placebo (adjusted mean[‡])<br>(95% CI) | −1.68[§]<br>(−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.
¶ 2-hour PPG level as a response to a 75-gram oral glucose tolerance test (OGTT).
# All randomized patients who took at least one dose of double-blind study medication during the short-term, double-blind period.
** p-value <0.05 versus placebo.
†† LOCF: last observation (after rescue) carried forward

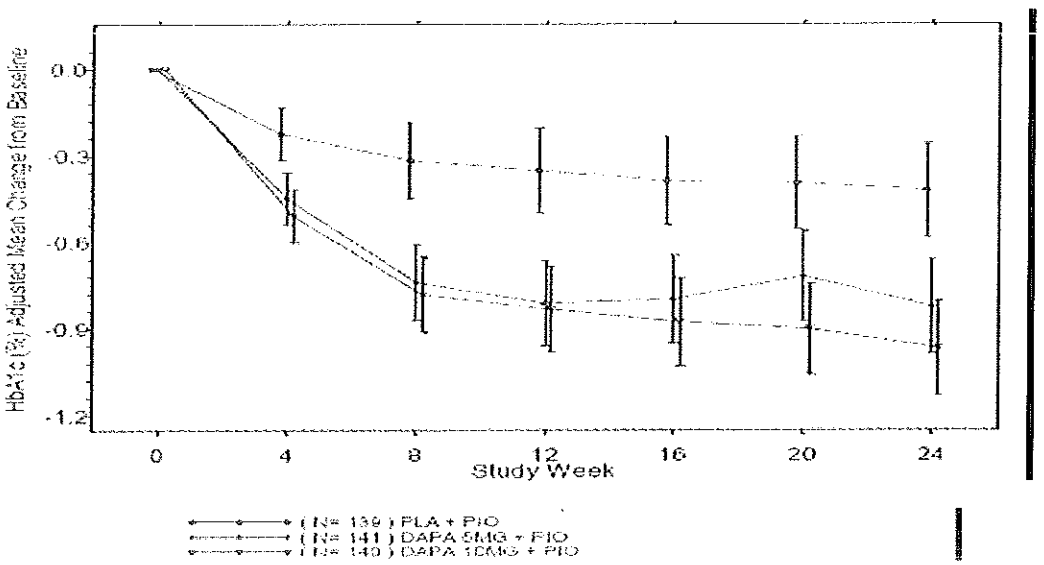
**Figure 8: Adjusted Mean Change from Baseline Over Time (LOCF) in HbA1c (%) in a 24-Week, Placebo-Controlled Study of FORXIGA in Combination with Sulfonylurea**

(Glimepiride AstraZeneca



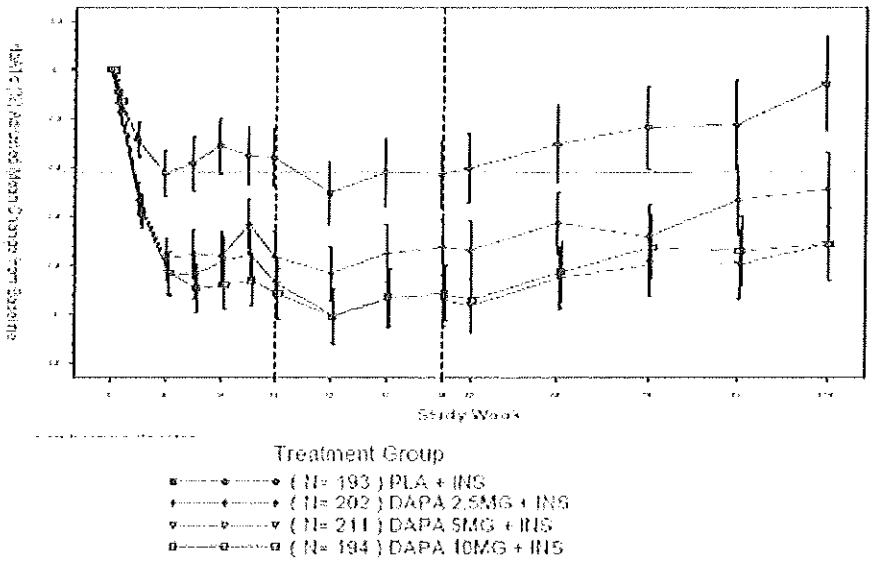

**Error bars represent 95% confidence intervals for the adjusted mean change from baseline**

**Figure 9: Adjusted Mean Change from Baseline Over Time (LOCF) in HbA1c (%) in a 24-Week Placebo-Controlled Study of FORXIGA in Combination with a Thiazolidinedione (pioglitazone)**




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

**Figure 10: Adjusted Mean Change from Baseline Over Time in HbA1c (%) in a 104-Week Placebo-controlled Study of FORXIGA in Combination with Insulin with or without up to 2 Oral Antidiabetic Therapies Excluding Data After Insulin Up-titration**




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

### Add-on to Sitagliptin Alone or in Combination with Metformin

A total of 452 patients with type 2 diabetes who were drug naive, or who were treated at entry with metformin or a DPP4 inhibitor alone or in combination, and had inadequate glycemic control (HbA1c ≥7.0% and ≤10.0% at randomization), participated in a 24-week, placebocontrolled study with a 24-week extension period to evaluate FORXIGA in combination with sitagliptin (a DPP4 inhibitor) with or without metformin.

Eligible patients were stratified based on the presence or absence of background metformin (≥1500 mg/day) and within each stratum were randomized to either FORXIGA 10 mg plus sitagliptin 100 mg once daily or placebo plus sitaglipitin 100 mg once daily. Endpoints were tested for FORXIGA 10 mg versus placebo for the total study group (sitagliptin with and without metformin) and for each stratum (sitagliptin alone or sitagliptin with metformin). Thirtyseven percent (37%) of patients were drug naive, 32% were on metformin alone, 13% were on aDPP4 inhibitor alone, and 18% were on a DPP4 inhibitor plus metformin. Dose titration of FORXIGA, sitagliptin or metformin was not permitted during the study.

In combination with sitagliptin (with and without metformin), FORXIGA 10 mg provided significant improvements in HbA1c, HbA1c in patients with baseline HbA1c ≥8%, and FPG, and significant reduction in body weight compared with the placebo plus sitagliptin (with or without metformin) and group at Week 24 (Table 7). These improvements were also seen in the stratum of patients who received FORXIGA 10 mg plus sitagliptin alone (n=110) compared with placebo plus sitagliptin alone (n=111), and the stratum of patients who received FORXIGA 10 mg plus sitagliptin and metformin (n=113) compared with placebo plus sitagliptin with metformin (n=113) (Table 8).

At Week 48, adjusted mean change from baseline in HbA1c, HbA1c in patients with HbA1c ≥8% at baseline, FPG, PPG, and body weight were −0.30%, −0.72%, −19.7 mg/dL, −43.0 mg/dL, and −2.03 kg, respectively, for patients treated with FORXIGA 10 mg plus sitagliptin with or without metformin, and 0.38%, 0.26%, 13.4 mg/dL,−12.1 mg/dL, and 0.18 kg for patients treated with placebo plus sitagliptin with or without metformin based on the longitudinal repeated measures analysis excluding data after rescue. At Week 48, for the stratum of patients without metformin, adjusted mean change from baseline in HbA1c for

patients treated with FORXIGA 10 mg plus sitagliptin was 0.00% and placebo plus sitagliptin was 0.85%; and for the stratum of patients with metformin, adjusted mean change from baseline in HbA1c for patients treated with FORXIGA 10 mg plus sitagliptin was −0.44% and placebo plus sitagliptin was 0.15% based on the longitudinal repeated measures analysis excluding data after rescue.

The proportion of patients at Week 24 and Week 48 who were rescued or discontinued for lack of glycemic control (adjusted for baseline HbA1c) was higher for sitagliptin with or without metformin (41.5% and 56.6%, respectively) than for FORXIGA with or without metformin (18.8% and 32.7%, respectively).

**Table 7: Results of 24 week (LOCF*) Placebo –controlled study of Forxiga in Add-on combination with sitagliptin with or without Metformin (Full Analysis Set and Strata without or with Metformin)**

| Efficacy Parameter | Forxiga 10 mg + Sitagliptin + or −Met | Placebo + Sitagliptin + or −Met | Forxiga 10 mg + Sitagliptin | Placebo + Sitaglipti n | Forxiga 10 mg + Sitagliptin +Met | Placebo + Sitagliptin +Met |
|---|---|---|---|---|---|---|
| | N=223† | N=224† | N=110† | N=111† | N=113† | N=113† |
| **HbA1c (%)** | | | | | | |
| Baseline (mean) | 7.90 | 7.97 | 7.99 | 8.07 | 7.80 | 7.87 |
| Change from baseline (adjusted mean‡) | −0.45 | 0.04 | −0.47 | 0.10 | −0.43 | −0.02 |
| Difference from Placebo(adjusted mean‡) (95% CI) | −0.48§ (−0.62, −0.34) | | −0.56§ (−0.79, −0.34) | | −0.40§ (−0.58, −0.23) | |
| Change from baseline in HbA1c in patients with baseline HbA1c ≥8% (adjusted mean‡) | −0.80§ (N= 94) | 0.03 (N= 99) | −0.81§ | 0.06 | −0.79§ | 0.0 |
| **FPG (mg/dL)** | | | | | | |
| Baseline (mean) | 161.7 | 163.1 | 157.3 | 161.5 | 165.9 | 164.7 |
| Change from baseline at Week 24 (adjusted mean‡) | −24.1 | 3.8 | −22.0 | 4.6 | −26.2 | 3.0 |
| Difference from placebo (adjusted mean‡) (95% CI) | 27.9§ (−34.5, −21.4) | | −26.6§ (−36.3, −16.85) | | −29.2§ (−38.0, −20.4) | |
| **Body Weight (kg)** | | | | | | |
| Baseline (mean) | 91.02 | 89.23 | 88.01 | 84.20 | 93.95 | 94.17 |
| Change from baseline (adjusted mean‡) | −2.14 | −0.26 | −1.91 | −0.06 | −2.35 | −0.47 |
| Difference from placebo (adjusted mean‡) (95% CI) | −1.89§ (−2.37, −1.40) | | −1.85§ (−2.47, −1.23) | | −1.87§ (−2.61, −1.13) | |

**Table 7: Results of 24 week (LOCF*) Placebo–controlled study of Forxiga in Add-on combination with sitagliptin with or without Metformin (Full Analysis Set and Strata without or with Metformin)**

| Efficacy | Forxiga | Placebo + | Forxiga | Placebo | Forxiga | Placebo |
|---|---|---|---|---|---|---|

| Parameter | 10 mg + Sitagliptin + or −Met | Sitagliptin + or −Met | 10 mg + Sitagliptin | + Sitagliptin | Sitagliptin +Met | Sitagliptin +Met |
|---|---|---|---|---|---|---|
| **Seated SBP at Week 8 in patients with baseline seated SBP ≥130 mmHg (mmHg)** | | | | | | |
| Baseline (mean) | 140.5 (N=111) | 139.3 (N=101) | 138.5 | 137.9 | 141.9 | 140.3 |
| Change from baseline (adjusted mean‡) | −6.0 | −5.1 | −6.6 | −4.2 | −5.3 | −5.5 |
| Difference from Placebo (adjusted mean‡) (95% CI) | −0.86 (−3.8, 2.0) | | −2.4 (−6.4,1.7) | | 0.2 (−3.85,4.32) | |
| **2-hourPPG¶ (mg/dL)** | | | | | | |
| Baseline (mean) | 227.8 | 226.3 | 225.3 | 231.2 | 230.2 | 221.0 |
| Change from baseline (adjusted mean‡) | −47.7 | −4.8 | −46.3 | −2.6 | −48.9 | −7.2 |
| Difference from placebo (adjusted mean‡) (95% CI) | −42.9 (−52.1, −33.8) | | −43.7 (−55.9, −31.5) | | −41.6 (−55.4, −27.8) | |
| **Patients with HbA1c decrease ≥ 0.7% (adjusted %)** | 35.4% | 16.6% | 42.8 | 17.2 | 28.0 | 16.0 |

* 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).

## 10.3 Supportive Studies

### Use in Patients with Type 2 Diabetes and Hypertension

In two 12-week, placebo-controlled studies, a total of 1062 patients with inadequately controlled type 2 diabetes and hypertension were treated with FORXIGA 10 mg or placebo. Patients with inadequately controlled hypertension (seated systolic blood pressure ≥140 and <165 mmHg, seated diastolic blood pressure ≥85 and <105 mmHg, and a 24-hour mean blood pressure of ≥130/80 mmHg) despite pre-existing stable treatment with an angiotensin-converting enzyme inhibitor (ACE) or angiotensin receptor blocker (ARB) (alone [Study 1] or in combination withan additional antihypertensive [Study 2]) as well as inadequate glycemic control (HbA1c ≥ 7.0% and ≤ 10.5%) despite pre-existing stable treatment with OADs or insulin (alone or in combination) prior to entry, were eligible for these studies. During the studies, no adjustments in antidiabetic and antihypertensive medications were allowed. Across the 2 studies, 527 patients were treated with FORXIGA 10 mg and 535 with placebo. Patients treated with FORXIGA 10 mg or placebo also received the following medications for blood

pressure control, which were balanced between treatment groups: ACE inhibitors (36%), thiazide diuretics (16%), calcium channel blockers (9%), and beta-blockers (6%).

At Week 12 for both studies, FORXIGA 10 mg plus usual treatment provided significant improvement in HbA1c and significant reduction in seated systolic blood pressure compared with placebo plus usual treatment (see Table 8). Consistent reductions were seen in mean 24 - hour ambulatory systolic blood pressure in patients treated with FORXIGA 10 mg treatment compared with placebo. There was a small reduction in mean seated diastolic blood pressure in patients treated with FORXIGA 10 mg that was not statistically significant compared with placebo.

**Table 8: Results at Week 12 in 2 Placebo-Controlled Studies of FORXIGA in Patients with Type 2 Diabetes and Hypertension**

| | Study 1 | | Study 2 | |
|---|---|---|---|---|
| **Efficacy Parameter** | **FORXIGA 10 mg + Usual Treatment N=302†** | **Placebo + Usual Treatment N=311†** | **FORXIGA 10 mg + Usual Treatment N=225†** | **Placebo + Usual Treatment N=224†** |
| **HbA1c (%) (LRM)*** | | | | |
| Baseline (mean) | 8.1 | 8.0 | 8.1 | 8.0 |
| Change from baseline (adjusted mean‡) | −0.6 | −0.1 | −0.6 | 0.0 |
| Difference from placebo (adjusted mean‡) (95% CI) | −0.5§ (−0.6, −0.3) | | −0.6§ (−0.8, −0.5) | |
| **Seated Systolic Blood Pressure (mmHg) (LRM)*** | | | | |
| Baseline (mean) | 149.8 | 149.5 | 151.0 | 151.3 |
| Change from baseline (adjusted mean‡) | −10.4 | −7.3 | −11.9 | −7.6 |
| Difference from placebo (adjusted mean‡) (95% CI) | −3.1¶ (−4.9, −1.2) | | −4.3¶ (−6.5, −2.0) | |

† All randomized patients who took at least one dose of double-blind study medication during the short-term, double-blind period.
‡ Least squares mean adjusted for baseline value.
§ p-value <0.0001.
¶ p-value <0.05.
# LOCF: last observation carried forward.

## Use in Patients with with Type 2 Diabetes and Cardiovascular Disease

In two 24-week, placebo-controlled studies with 78-week extension periods, a total of 1887 patients with type 2 diabetes and CVD were treated with FORXIGA 10 mg or placebo.

Patients with established CVD and inadequate glycemic control (HbA1c ≥7.0% and ≤10.0%), despite pre-existing, stable treatment with OADs or insulin (alone or in combination) prior to entry, were eligible for these studies and were stratified according to age (<65 years or ≥65 years), insulin use (no or yes), and time from most recent qualifying cardiovascular event (>1

year or <1 year prior to enrollment). Across the 2 studies, 942 patients were treated with FORXIGA 10 mg and 945 with placebo. Ninety-six percent (96%) of patients treated with FORXIGA 10 mg across the 2 studies had hypertension at entry, the majority for more than 10 years duration; the most common qualifying cardiovascular events were coronary heart disease (75%) or stroke (22%). Approximately 19% of patients received loop diuretics at entry and 15% had congestive heart failure (2% had NYHA Class III). Approximately 37% of patients treated with FORXIGA 10 mg also received metformin plus one additional OAD (sulfonylurea, thiazolidinedione, DPP4-inhibitor, or other OAD with or without insulin at entry), 39% received insulin plus at least one OAD, and 18% received insulin alone.

At Week 24 for both studies, when added to pre-existing antidiabetic treatments, treatments with FORXIGA 10 mg provided significant improvement to coprimary endpoints of HbA1c and composite clinical benefit. Composite clinical benefit compared with placebo was defined as the proportion of patients with an absolute drop from baseline of 0.5% in HbA1c, and a relative drop from baseline of at least 3% in total body weight, and an absolute drop from baseline of at least 3 mmHg in seated SBP (Table 9). Significant reductions in total body weight and seated systolic blood pressure were also seen in patients treated with FORXIGA 10 mg compared with placebo.

At Week 52 and Week 104 for Study 1, adjusted mean change from baseline in HbA1c, seated systolic blood pressure, and adjusted percent change from baseline in body weight were −0.44% and −0.41%, −3.40 mmHg and −2.64 mmHg, and −2.89% and −3.53%, respectively, for patients treated with FORXIGA 10 mg plus usual treatment based on the longitudinal repeated measures analysis. Corresponding numbers for patients treated with placebo plus usual treatment were 0.22% and 0.50%, 0.18 mmHg and 1.54 mmHg, and −0.29% and −0.02%. At Week 52 and Week 104, percent composite clinical benefit was still higher in the FORXIGA 10 mg group (6.6% and 3.8%) than in the placebo group (0.7% and 0.5%).

At Week 24, Week 52, and Week 104 for Study 1, the proportion of patients who were rescued for lack of glycemic control (adjusted for baseline HbA1c) was higher in the placebo plus usual treatment group (24.0%, 51.8%, and 57.3%, respectively) than in the FORXIGA 10 mg plus usual treatment group (7.8%, 24.6%, and 31.8%, respectively).

At Week 52 and Week 104 for Study 2, adjusted mean change from baseline in HbA1c, seated systolic blood pressure, and adjusted percent change from baseline in body weight were −0.47% and −0.37%, −3.56 mmHg and −1.96 mmHg , and −3.20% and −3.51%, respectively, for patients treated with FORXIGA 10 mg plus usual treatment based on the longitudinal repeated measures analysis. Corresponding numbers for patients treated with placebo plus usual treatment were 0.03% and −0.18%, −0.91 mmHg and −0.37 mmHg , and −1.12% and −0.65%.

At Week 52 and Week 104, percent composite clinical benefit was still higher in the FORXIGA 10 mg group (10.6% and 4.2%) than in the placebo group (3.1% and 1.1%). At Week 24, Week 52, and Week 104 for Study 2, the proportion of patients who were rescued for lack of glycemic control (adjusted for baseline HbA1c) was higher in the placebo plus usual treatment group (22.3%, 43.6%, and 50.5%, respectively) than in the FORXIGA 10 mg plus usual treatment group (7.6%, 18.7%, and 27.5%, respectively).

**Table 9: Results at week 24 (LOCF*) in two Placebo –controlled studies comparing Forxiga to Placebo in Diabetic Patients with Cardiovascular Disease.**

| | Study 1 | | Study 2 | |
|---|---|---|---|---|
| **Efficacy Parameter** | **Forxiga 10 mg + Usual** | **PLACEBO +** | **Forxiga** | **PLACEBO +** |

| | Treatment | Usual Treatment | 10 mg + Usual Treatment | Usual Treatment |
|---|---|---|---|---|
| | N=455[†] | N=459[†] | N=480[†] | N=482[†] |
| **HbA1c (%)** | | | | |
| Baseline mean | 8.18 | 8.08 | 8.04 | 8.07 |
| Change from baseline (adjusted mean[‡]) | −0.38 | 0.08 | −0.33 | 0.07 |
| Difference from placebo (adjusted mean[‡]) (95% CI) | −0.46[§] (−0.56, −0.37) | | −0.40[§] (−0.50, −0.30) | |
| **Responders of Composite Clinical Benefit (%)** | 11.7 | 0.9 | 10.0 | 1.9 |
| Difference from placebo (adjusted %) | 9.9[§] | | 7.0[§] | |
| **Components of Composite Endpoint (%)** [250,251] | | | | |
| Patients with absolute reduction HbA1c ≥0.5% (adjusted %) | 46.2 | 19.7 | 42.2 | 21.2 |
| Patients with body weight decrease of at least 3% from baseline (adjusted %) | 40.0 | 13.9 | 41.3 | 15.4 |
| Patients with absolute reduction in SBP ≥ 3 mmHg (adjusted %) | 49.4 | 41.4 | 46.3 | 40.7 |
| **Body Weight (kg)** | | | | |
| Baseline mean | 92.63 | 93.59 | 94.53 | 93.22 |
| Change from baseline (adjusted mean[‡]) | −2.56 | −0.30 | −2.53 | −0.61 |
| Difference from placebo (adjusted percent[‡]) (95% CI) | −2.27[§] (−2.64, −1.89) | | −1.93[§] (−2.31, −1.54) | |
| Body weight decrease of at least 5% in patients with baseline BMI ≥27 kg/m2 (%) | 16.5[§] | 4.0 | 18.4[§] | 4.8 |
| **Seated Systolic Blood Pressure (mmHg)** | | | | |
| Change from baseline at Week 24 (adjusted mean[‡]) | −2.99 | −1.03 | −2.70 | 0.32 |

**Table 9: Results at week 24 (LOCF*) in two Placebo –controlled studies comparing FORXIGA to Placebo in Patients with Type 2 Diabetes and Cardiovascular Disease.**

| | Study 1 | | Study 2 | |
|---|---|---|---|---|
| **Efficacy Parameter** | **Forxiga 10 mg + Usual Treatment** | **PLACEBO + Usual Treatment** | **Forxiga 10 mg + Usual Treatment** | **PLACEBO + Usual Treatment** |
| Difference from placebo (adjusted mean[‡]) | −1.95[¶] | | −3.02[¶] (−4.59, −1.46) | |
| Change from baseline seated SBP (mmHg) at week 8 in patients with baseline SBP ≥130 mmHg (adjusted mean[‡]) | - | - | −5.33[¶] | −1.89 |

AstraZeneca

* 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.
¶ p-value <0.05

At week 24 patients treated with FORXIGA 10 mg in the pre-defined age groups (<65 and ≥65 years of age) also showed significant reduction in the coprimary endpoints of HbA1c and composite clinical benefit compared with placebo in both studies. A significant improvement in total body weight was also seen in both age groups and a significant reduction of seated SBP in patients <65 years treated with FORXIGA 10 mg compared with placebo at Week 24. These effects were maintained at Week 52 and Week 104

**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 in 182 patients with Type 2 diabetes. Treatment with . FORXIGA 10 mg added on to metformin over a 24-week period provided significant improvements compared with placebo plus metformin, respectively, in body weight (mean change from baseline: −2.96 kg vs −0.88 kg); waist circumference (mean change from baseline: −2.51 cm vs −0.99 cm), and body-fat mass as measured by DXA (mean change from baseline −2.22 kg vs −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. Week 24 was analyzed using last observation carried forward (LOCF) analysis including data after rescue.

At Week 24, 2 patients (2.2%) in the placebo plus metformin group and no patients in the FORXIGA 10 mg plus metformin group were rescued for lack of glycemic control.

At Week 50 and Week 102, improvements were sustained in the FORXIGA 10 mg added on to metformin group compared with the placebo plus metformin group for body weight (adjusted mean change from baseline at Week 50: −4.39 kg vs −2.03 kg; adjusted mean change from baseline at Week 102: −4.54 kg vs −2.12 kg), waist circumference (adjusted mean change from baseline at Week 50: −5.0 cm vs −3.0 cm; adjusted mean change from baseline at Week 102: −5.0 cm vs −2.9 cm ), and body-fat mass as measured by DXA at Week 102 (mean change from baseline: −2.80 kg vs −1.46 kg) based on the longitudinal repeated measures analysis including data after rescue. In an MRI substudy at Weeks 50 and 102, FORXIGA plus metformin treatment showed a numerical decrease in visceral adipose tissue compared with placebo plus metformin treatment (adjusted mean change from baseline at Week 50: −120.0 cm3 vs 61.5 cm3; adjusted mean change from baseline at Week 102: −214.9 cm3 vs −22.3 cm3).

The proportion of patients at Week 50 (unadjusted for baseline HbA1c) and Week 102 (adjusted for baseline HbA1c) who were rescued or discontinued for lack of glycemic control was higher in the placebo plus metformin group (6.6% and 33.2%, respectively) than in the FORXIGA 10 mg plus metformin group (2.2% and 13.5%, respectively)

In an extension of this study to Week 50, there was no change in bone mineral density (BMD) for the lumbar spine, femoral neck, or total hip seen in either treatment group (mean decrease from baseline for all anatomical regions <0.5%). There was also no change in BMD in either treatment group up to Week 102 (mean decrease from baseline for all anatomical regions <1.0%). There were no clinically meaningful changes in markers of bone resorption or bone formation.

### Use in Patients with Type 2 Diabetes and 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 at Week 24. Similar results were seen at Week 104 (see section 5.11).

## 10.4 Blood Pressure

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

For the two dedicated studies in patients with type 2 diabetes and CVD, treatment with FORXIGA 10 mg significantly decreased the placebo-corrected systolic blood pressure an average of 2.0 to 3.0 mmHg from baseline at Week 24 (see Table 9) and maintained through Week 104.

For the two dedicated studies in patients with type 2 diabetes and hypertension, treatment with FORXIGA 10 mg significantly decreased the placebo-corrected systolic blood pressure an average of 3.0 to 4.0 mmHg from baseline at Week 12 (see Table 8).

# 11 NON-CLINICAL SAFETY

## 11.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Dapagliflozin did not induce tumors in either mice or rats at any of the doses evaluated in 2-year carcinogenicity studies. Oral doses in mice consisted of 5, 15, and 40 mg/kg/day in males and 2, 10, and 20 mg/kg/day in females, and oral doses in rats were 0.5, 2, and 10 mg/kg/day for both males and females. The highest doses evaluated in mice were equivalent to AUC exposure multiples of approximately 72× (males) and 105× (females) the human AUC at MRHD of 10 mg/day. In rats, AUC exposures were approximately 131× (males) and 186× (females) the human AUC at the MRHD.

Dapagliflozin was negative in the Ames mutagenicity assay and was positive in an in vitro clastogenicity assay, but only in the presence of S9 activation and at concentrations ≥100 µg/mL. Importantly, dapagliflozin was negative for clastogenicity in vivo in a series of studies evaluating micronuclei or DNA repair in rats at exposure multiples >2100× the human exposure at the MRHD. These studies, along with the absence of tumor findings in the rat and mouse carcinogenicity studies, support that dapagliflozin does not represent a genotoxic risk to humans.

Dapagliflozin-related gene transcription changes were evaluated in AstraZeneca and skeletal muscle of Zucker Diabetic Fatty (ZDF) rats treated daily with dapagliflozin for 5 weeks.323 These organs were specifically selected as they represent target organs in the treatment of diabetes. There was no evidence that dapagliflozin caused transcriptional changes that are predictive of tumor promoters.

Dapagliflozin and its primary human metabolite (3-O-glucuronide) did not enhance the *in vitro* growth of six human urinary bladder transitional cell carcinomas (TCC) cell lines at concentrations ≥100× human Cmax at the MRHD. In a mouse xenograft study, dapagliflozin administered daily to male and female nude mice implanted with human TCC tumors did not significantly enhance the size of tumors at exposures up to 75× and up to 0.9× clinical exposures at the MRHD for dapagliflozin and its 3-O-glucuronide metabolite, respectively. These studies provide evidence that dapagliflozin and its primary human metabolite do not enhance urinary bladder tumor growth.

In a 15-month phenotyping study, there was no evidence of any difference in survival, body weights, clinical pathology parameters, or histopathologic findings observed between SGLT2 KO mice and their wild-type (WT) counterparts.328 SGLT2 KO mice had glucosuria, unlike the WT mice. Despite a lifetime of glucosuria, there was no evidence of any alteration of renal function or proliferative changes observed in the kidneys or urinary bladders of SGLT2 KO mice. This data strongly suggests that high levels of urinary glucose do not induce urinary tract tumors or accelerate age-related urinary tract pathology.

In a study of fertility and early embryonic development in rats, doses of 15, 75, or 300/210 mg/kg/day dapagliflozin were administered to males (the 300 mg/kg/day dose was lowered to 210 mg/kg/day after 4 days), and doses of 3, 15, or 75 mg/kg/day were administered to females. Dapagliflozin had no effects on mating, fertility, or early embryonic development in treated males or females at any dose tested (at exposure multiples ≤1708× and 998× the MRHD in males and females, respectively). However, at 300/210 mg/kg/day, seminal vesicle and epididymal weights were reduced; sperm motility and sperm counts were reduced; and there were low numbers of morphologically abnormal sperm.

## 11.2 Teratogenicity and Impairment of Early Development

Direct administration of dapagliflozin to weanling juvenile rats and indirect exposure during late pregnancy and lactation (time periods corresponding to the second and third trimesters of pregnancy with respect to human renal maturation) are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny.

In a juvenile toxicity study, when dapagliflozin was dosed directly to young rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg/kg/day, renal pelvic and tubular dilatations were reported at all dose levels; pup exposures at the lowest dose tested were ≥15× the MRHD. These findings were associated with dose-related increases in kidney weight and macroscopic kidney enlargement observed at all doses. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1-month recovery period.

In a separate study of prenatal and postnatal development, maternal rats were dosed from gestation day (GD) 6 through PND 21 (also at 1, 15, or 75 mg/kg/day), and pups were indirectly exposed in utero and throughout lactation. (A satellite study was conducted to assess dapagliflozin exposures in milk and pups.) Increased incidence or severity of renal pelvic

dilatation was again observed in adult offspring of treated dams, although only at 10 mg/kg/day (associated maternal and pup dapagliflozin exposures were 1415× and 137×, respectively, the human values at the MRHD). Additional developmental toxicity was limited to dose-related reductions in pup body weights and observed only at doses ≥15 mg/kg/day (associated with pup exposures that are ≥29× the human values at the MRHD). Maternal toxicity was evident only at 75 mg/kg/day, and limited to transient reductions in body weight and food consumption at dose initiation. The no-adverse-effect level (NOAEL) for developmental toxicity, 1 mg/kg/day, is associated with a maternal systemic exposure multiple that is approximately 19× the human value at the MRHD.

In additional studies of embryo-fetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the major periods of organogenesis in each species. Neither maternal nor developmental toxicities were observed in rabbits at any dose tested (20, 60, or 180 mg/kg/day); 180 mg/kg/day is associated with a systemic exposure multiple of approximately 1191× the MRHD. In rats, dapagliflozin was neither embryolethal nor teratogenic at doses up to 75 mg/kg/day (1441× the MRHD). Doses ≥150 mg/kg/day (≥2344× the human values at the MRHD) were associated with both maternal and developmental toxicities. Maternal toxicity included mortality, adverse clinical signs, and decrements in body weight and food consumption. Developmental toxicity consisted of increased embryo-fetal lethality, increased incidences of fetal malformations and skeletal variations, and reduced fetal body weights. Malformations included a low incidence of great vessel malformations, fused ribs and vertebral centras, and duplicated manubria and sternal centra. Variations were primarily reduced ossifications.

## 11.3 Animal Toxicology

Most of the effects observed in pivotal repeat-dose toxicity studies in both rats and dogs were considered to be secondary to pharmacologically mediated increases in urinary glucose, and included decreases in body weights and/or body weight gains, increased food consumption, andincreases in urine volumes due to osmotic diuresis. Dapagliflozin was well tolerated when given orally to rats for up to 6 months at doses of ≤25 mg/kg/day (≥346×the human exposures at the MRHD) and in dogs for up to 12 months at doses of ≤120 mg/kg/day (≥3200× the human exposures at the MRHD). Also, single-dose studies with dapagliflozin indicated that the dapagliflozin 3-O-glucuronide metabolite would have been formed in both rat and dog toxicity studies at exposure levels (AUCs) that are greater than, or approximately equal to, anticipated human dapagliflozin 3-O-glucuronide exposures following administration of dapagliflozin at the MRHD. In rats, the most noteworthy nonclinical toxicity finding of increased trabecular bone and tissue mineralization (associated with increased serum calcium) was only observed at highexposure multiples (≥2100× based on human exposures at the MRHD). Despite achieving exposure multiples of ≥3200× the human exposure at the MRHD, there was no dose-limiting or target-organ toxicities identified in the 12-month dog study.

# 12 PHARMACEUTICAL PROPERTIES

## 12.1 List of Excipients

Each film-coated tablet of FORXIGA contains 5 mg or 10 mg of dapagliflozin and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, crospovidone, silicon dioxide, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and yellow iron oxide.

AstraZeneca

## 12.2 Incompatibilities
Not applicable.

## 12.3 Shelf Life

Refer Outer Carton

## 12.4 Storage

Store below 30°C.

## 12.5 Presentation:
FORXIGA (dapagliflozin propanediol) 5-mg tablets are yellow, biconvex, round, filmcoated tablets with "5" engraved on one side and "1427" engraved on the other side.

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

## 12.6 Special Instructions for Use, Handling, and Disposal
No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

**Forxiga™ is a trademark of AstraZeneca Group Companies.**

## Manufactured by :
Refer to outer carton

**For Information please contact**

**AstraZeneca Pharma India Limited**
Block N1, 12th Floor
Manyata Embassy Business Park
Rachenahalli, Outer Ring Road
Bangalore – 560045

**Proposed Prescribing Information Version 3, dated 17th Feb 2015**