

# Forxiga Film-coated Tablets 5 mg, 10 mg

## 1 INDICATIONS AND USAGE

Type 2 diabetes mellitus [see *Clinical Studies (14)*].

### 1.1 Limitation of Use

Forxiga is not recommended for patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dosing

Forxiga can be used as monotherapy or as combination therapy with metformin, sulfonylurea, thiazolidinedione, DPP-4 inhibitors (with/without metformin), metformin plus a sulfonylurea, insulin, or GLP-1 receptor agonist with metformin as an adjunct to diet and exercise to improve glycemic control on patients with type 2 diabetes mellitus. Please refer to *Clinical Studies (14)* for the information of combination with other antidiabetic drugs.

The recommended starting dose of Forxiga is 5 mg once daily, taken in the morning, with or without food. In patients tolerating Forxiga 5 mg once daily who require additional glycemic control, the dose can be increased to 10 mg once daily.

In patients with volume depletion, correcting this condition prior to initiation of Forxiga is recommended [see *Warnings and Precautions (5.1)*, *Use in Specific Populations (8.5, 8.6)*, and *Patient Counseling Information (17)*].

### 2.2 Patients with Renal Impairment

Assessment of renal function is recommended prior to initiation of Forxiga therapy and periodically thereafter.

Forxiga should not be initiated in patients with an eGFR less than 60 mL/min/1.73 m<sup>2</sup>.

No dose adjustment is needed in patients with mild renal impairment (eGFR of 60 mL/min/1.73 m<sup>2</sup> or greater).

Forxiga should be discontinued when eGFR is persistently less than 60 mL/min/1.73 m<sup>2</sup> [see *Warnings and Precautions (5.3)* and *Use in Specific Populations (8.6)*].

### **3 DOSAGE FORMS AND STRENGTHS**

- Forxiga 5 mg tablets are yellow, biconvex, round, film-coated tablets with “5” engraved on one side and “1427” engraved on the other side.
- Forxiga 10 mg tablets are yellow, biconvex, diamond-shaped, film-coated tablets with “10” engraved on one side and “1428” engraved on the other side.

### **4 CONTRAINDICATIONS**

- History of a serious hypersensitivity reaction to Forxiga [see *Adverse Reactions (6.1)*].
- Severe renal impairment, end-stage renal disease (ESRD), or patients on dialysis [see *Use in Specific Populations (8.6)*].

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Hypotension**

Forxiga causes intravascular volume contraction. Symptomatic hypotension can occur after initiating Forxiga [see *Adverse Reactions (6.1)*] particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m<sup>2</sup>), elderly patients, or patients on loop diuretics. Before initiating Forxiga in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms of hypotension after initiating therapy.

#### **5.2 Ketoacidosis**

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium-glucose cotransporter 2 (SGLT2) inhibitors, including Forxiga. Fatal cases of ketoacidosis have been reported in patients taking Forxiga. Forxiga is not indicated for the treatment of patients with type 1 diabetes mellitus [see *Indications and Usage (1.1)*].

Patients treated with Forxiga who present with signs and symptoms consistent with ketoacidosis,

including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are below 14 mmol/l (250 mg/dl). If ketoacidosis is suspected, Forxiga should be discontinued, the patient should be evaluated and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

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

Before initiating Forxiga, patients should be considered with the situation or history as above mentioned. Forxiga should be used with caution in these patients, and evaluate the necessity for monitoring the symptoms of ketoacidosis. In patients treated with Forxiga consider monitoring for ketoacidosis and temporarily discontinuing Forxiga in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

### **5.3 Acute Kidney Injury and Impairment in Renal Function**

Forxiga causes intravascular volume contraction [see *Warning and Precautions (5.1)*], and can cause renal impairment [see *Adverse Reactions (6.1)*]. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving Forxiga; some reports involved patients younger than 65 years of age.

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

Forxiga increases serum creatinine and decreases eGFR. Elderly patients and patients with impaired renal function may be more susceptible to these changes. Adverse reactions related to renal function can occur after initiating Forxiga [see *Adverse Reactions (6.1)*]. Renal function should be evaluated prior to initiation of Forxiga and monitored periodically thereafter. Use of Forxiga is not recommended in patients with an eGFR persistently between 30 and less than 60

mL/min/1.73 m<sup>2</sup> and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m<sup>2</sup> [see *Dosage and Administration (2.2)*, *Contraindications (4)*, *Use in Specific Populations (8.6)*].

## **5.4 Urosepsis and Pyelonephritis**

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

## **5.5 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues**

Insulin and insulin secretagogues are known to cause hypoglycemia. Forxiga can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue [see *Adverse Reactions (6.1)*]. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when these agents are used in combination with Forxiga.

## **5.6 Genital Mycotic Infections**

Forxiga increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections [see *Adverse Reactions (6.1)*]. Monitor and treat appropriately.

## **5.7 Increases in Low-Density Lipoprotein Cholesterol (LDL-C)**

Increases in LDL-C occur with Forxiga [see *Adverse Reactions (6.1)*]. Monitor LDL-C and treat per standard of care after initiating Forxiga.

## **5.8 Bladder Cancer**

Across 22 clinical studies, newly diagnosed cases of bladder cancer were reported in 10/6045 patients (0.17%) treated with Forxiga and 1/3512 patient (0.03%) treated with placebo/comparator. After excluding patients in whom exposure to study drug was less than one year at the time of diagnosis of bladder cancer, there were 4 cases with Forxiga and no cases with placebo/comparator. Bladder cancer risk factors and hematuria (a potential indicator of pre-existing tumors) were balanced between treatment arms at baseline. There were too few cases to determine whether the emergence of these events is related to Forxiga.

There are insufficient data to determine whether Forxiga has an effect on pre-existing bladder tumors. Consequently, Forxiga should not be used in patients with active bladder cancer. In patients with prior history of bladder cancer, the benefits of glycemic control versus unknown risks for cancer recurrence with Forxiga should be considered.

## 5.9 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Forxiga.

## 6 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Hypotension [see *Warnings and Precautions (5.1)*]
- Ketoacidosis [see *Warnings and Precautions (5.2)*]
- Acute Kidney Injury and Impairment in Renal Function [see *Warnings and Precautions (5.3)*]
- Urosepsis and Pyelonephritis [see *Warnings and Precautions (5.4)*]
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues [see *Warnings and Precautions (5.5)*]
- Genital Mycotic Infections [see *Warnings and Precautions (5.6)*]
- Increases in Low-Density Lipoprotein Cholesterol (LDL-C) [see *Warnings and Precautions (5.7)*]
- Bladder Cancer [see *Warnings and Precautions (5.8)*]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

#### Pool of 12 Placebo-Controlled Studies for Forxiga 5 and 10 mg

The data in Table 1 is derived from 12 placebo-controlled studies ranging from 12 to 24 weeks. In 4 studies Forxiga was used as monotherapy, and in 8 studies Forxiga was used as add-on to background antidiabetic therapy or as combination therapy with metformin [see *Clinical Studies (14)*].

These data reflect exposure of 2338 patients to Forxiga with a mean exposure duration of 21 weeks. Patients received placebo (N=1393), Forxiga 5 mg (N=1145), or Forxiga 10 mg (N=1193) once daily. The mean age of the population was 55 years and 2% were older than 75 years of age. Fifty percent (50%) of the population were male; 81% were White, 14% were Asian, and 3% were Black or African American. At baseline, the population had diabetes for an average of 6 years, had a mean hemoglobin A1c (HbA1c) of 8.3%, and 21% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired in 92% of patients and moderately impaired in 8% of patients (mean eGFR 86 mL/min/1.73 m<sup>2</sup>).

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

**Table 1: Adverse Reactions in Placebo-Controlled Studies Reported in  $\geq 2\%$  of Patients Treated with Forxiga**

Adverse Reaction	% of Patients		
	Pool of 12 Placebo-Controlled Studies		
	Placebo N=1393	Forxiga 5 mg N=1145	Forxiga 10 mg N=1193
Female genital mycotic infections*	1.5	8.4	6.9
Nasopharyngitis	6.2	6.6	6.3
Urinary tract infections <sup>†</sup>	3.7	5.7	4.3
Back pain	3.2	3.1	4.2
Increased urination <sup>‡</sup>	1.7	2.9	3.8
Male genital mycotic infections <sup>§</sup>	0.3	2.8	2.7
Nausea	2.4	2.8	2.5
Influenza	2.3	2.7	2.3
Dyslipidemia	1.5	2.1	2.5
Constipation	1.5	2.2	1.9
Discomfort with urination	0.7	1.6	2.1
Pain in extremity	1.4	2.0	1.7

\* Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for females: vulvovaginal mycotic infection, vaginal infection, vulvovaginal candidiasis, vulvovaginitis, genital infection, genital candidiasis, fungal genital infection, vulvitis, genitourinary tract infection, vulval abscess, and vaginitis bacterial. (N for females: Placebo=677, Forxiga 5 mg=581, Forxiga 10 mg=598).

<sup>†</sup> Urinary tract infections include the following adverse reactions, listed in order of frequency reported: urinary tract infection, cystitis, *Escherichia* urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection, and prostatitis.

<sup>‡</sup> Increased urination includes the following adverse reactions, listed in order of frequency reported: pollakiuria, polyuria, and urine output increased.

<sup>§</sup> Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for males: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection male, penile infection, balanoposthitis, balanoposthitis infective, genital infection, posthitis. (N for males: Placebo= 716,

Forxiga 5 mg=564, Forxiga 10 mg=595).

## Pool of 13 Placebo-Controlled Studies for Forxiga 10 mg

The safety and tolerability of Forxiga 10 mg was also evaluated in a larger placebo-controlled study pool. This pool combined 13 placebo-controlled studies, including 3 monotherapy studies, 9 add-on to background antidiabetic therapy studies, and an initial combination with metformin study. Across these 13 studies, 2360 patients were treated once daily with Forxiga 10 mg for a mean duration of exposure of 22 weeks. The mean age of the population was 59 years and 4% were older than 75 years. Fifty-eight percent (58%) of the population were 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, had a mean HbA1c of 8.2%, and 30% had established microvascular disease. Baseline renal function was normal or mildly impaired in 88% of patients and moderately impaired in 11% of patients (mean eGFR 82 mL/min/1.73 m<sup>2</sup>).

## Volume Depletion

Forxiga causes an osmotic diuresis, which may lead to reductions in intravascular volume. Adverse reactions related to volume depletion (including reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension) are shown in Table 2 for the 12-study and 13-study, short-term, placebo-controlled pools [see *Warnings and Precautions (5.1)*].

**Table 2: Adverse Reactions of Volume Depletion\* in Clinical Studies with Forxiga**

	Pool of 12 Placebo-Controlled Studies			Pool of 13 Placebo-Controlled Studies	
	Placebo	Forxiga 5 mg	Forxiga 10 mg	Placebo	Forxiga 10 mg
<b>Overall population N (%)</b>	N=1393 5 (0.4%)	N=1145 7 (0.6%)	N=1193 9 (0.8%)	N=2295 17 (0.7%)	N=2360 27 (1.1%)
<b>Patient Subgroup n (%)</b>					
Patients on loop diuretics	n=55 1 (1.8%)	n=40 0	n=31 3 (9.7%)	n=267 4 (1.5%)	n=236 6 (2.5%)
Patients with moderate renal impairment with eGFR ≥30 and <60 mL/min/1.73 m <sup>2</sup>	n=107 2 (1.9%)	n=107 1 (0.9%)	n=89 1 (1.1%)	n=268 4 (1.5%)	n=265 5 (1.9%)
Patients ≥65 years of age	n=276 1 (0.4%)	n=216 1 (0.5%)	n=204 3 (1.5%)	n=711 6 (0.8%)	n=665 11 (1.7%)

\* Volume depletion includes reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension.

## Impairment of Renal Function

Use of Forxiga was associated with increases in serum creatinine and decreases in eGFR (see Table 3). In patients with normal or mildly impaired renal function at baseline, serum creatinine and eGFR returned to baseline values at Week 24. Renal-related adverse reactions, including

renal failure and blood creatinine increase, were more frequent in patients treated with Forxiga (see Table 4). Elderly patients and patients with impaired renal function were more susceptible to these adverse reactions (see Table 4). Sustained decreases in eGFR were seen in patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m<sup>2</sup>).

**Table 3: Changes in Serum Creatinine and eGFR Associated with Forxiga in the Pool of 12 Placebo-Controlled Studies and Moderate Renal Impairment Study**

		Pool of 12 Placebo-Controlled Studies		
		Placebo N=1393	Forxiga 5 mg N=1145	Forxiga 10 mg N=1193
Baseline Mean	Serum Creatinine (mg/dL)	0.853	0.860	0.847
	eGFR (mL/min/1.73 m <sup>2</sup> )	86.0	85.3	86.7
Week 1 Change	Serum Creatinine (mg/dL)	-0.003	0.029	0.041
	eGFR (mL/min/1.73 m <sup>2</sup> )	0.4	-2.9	-4.1
Week 24 Change	Serum Creatinine (mg/dL)	-0.005	-0.001	0.001
	eGFR (mL/min/1.73 m <sup>2</sup> )	0.8	0.8	0.3
		Moderate Renal Impairment Study		
		Placebo N=84	Forxiga 5 mg N=83	Forxiga 10 mg N=85
Baseline Mean	Serum Creatinine (mg/dL)	1.46	1.53	1.52
	eGFR (mL/min/1.73 m <sup>2</sup> )	45.6	44.2	43.9
Week 1 Change	Serum Creatinine (mg/dL)	0.01	0.13	0.18
	eGFR (mL/min/1.73 m <sup>2</sup> )	0.5	-3.8	-5.5
Week 24 Change	Serum Creatinine (mg/dL)	0.02	0.08	0.16
	eGFR (mL/min/1.73 m <sup>2</sup> )	0.03	-4.0	-7.4
Week 52 Change	Serum Creatinine (mg/dL)	0.10	0.06	0.15
	eGFR (mL/min/1.73 m <sup>2</sup> )	-2.6	-4.2	-7.3

**Table 4: Proportion of Patients with at Least One Renal Impairment- Related Adverse Reaction**

Baseline Characteristic	Pool of 6 Placebo-Controlled Studies (up to 104 weeks)*			Pool of 9 Placebo-Controlled Studies (up to 104 weeks)†	
	Placebo	Forxiga 5 mg	Forxiga 10 mg	Placebo	Forxiga 10 mg
Overall population	n=785	n=767	n=859	n=1956	n=2026
Patients (%) with at least one event	13 (1.7%)	14 (1.8%)	16 (1.9%)	82 (4.2%)	136 (6.7%)
65 years of age and older	n=190	n=162	n=159	n=655	n=620
Patients (%) with at least one event	4 (2.1%)	5 (3.1%)	6 (3.8%)	52 (7.9%)	87 (14.0%)
eGFR ≥30 and <60 mL/min/1.73 m <sup>2</sup>	n=77	n=88	n=75	n=249	n=251
Patients (%) with at least one event	5 (6.5%)	7 (8.0%)	9 (12.0%)	40 (16.1%)	71 (28.3%)
65 years of age and older and eGFR ≥30 and <60 mL/min/1.73 m <sup>2</sup>	n=41	n=43	n=35	n=141	n=134
Patients (%) with at least one event	2 (4.9%)	3 (7.0%)	4 (11.4%)	27 (19.1%)	47 (35.1%)

\* Subset of patients from the pool of 12 placebo-controlled studies with long-term extensions.

† Subset of patients from the pool of 13 placebo-controlled studies with long-term extensions.



The safety of Forxiga was evaluated in a study of patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m<sup>2</sup>) [see *Clinical Studies (14)*]. In this study 13 patients experienced bone fractures for treatment durations up to 104 weeks. No fractures occurred in the placebo group, 5 occurred in the Forxiga 5 mg group, and 8 occurred in the Forxiga 10 mg group. Eight of these 13 fractures were in patients who had a baseline eGFR of 30 to 45 mL/min/1.73 m<sup>2</sup>. Eleven of the 13 fractures were reported within the first 52 weeks. There was no apparent pattern with respect to the anatomic site of fracture.

## Hypoglycemia

The frequency of hypoglycemia by study [see *Clinical Studies (14)*] is shown in Table 5. Hypoglycemia was more frequent when Forxiga was added to sulfonylurea or insulin [see *Warnings and Precautions (5.5)*].

**Table 5: Incidence of Major\* and Minor<sup>†</sup> Hypoglycemia in Controlled Clinical Studies**

	Placebo/Active Control	Forxiga 5 mg	Forxiga 10 mg
<b>Monotherapy* (24 weeks)</b>	<b>N=75</b>	<b>N=64</b>	<b>N=70</b>
Major [n (%)]	0	0	0
Minor [n (%)]	0	0	0
<b>Add-on to Metformin* (24 weeks)</b>	<b>N=137</b>	<b>N=137</b>	<b>N=135</b>
Major [n (%)]	0	0	0
Minor [n (%)]	0	2 (1.5)	1 (0.7)
<b>Active Control Add-on to Metformin versus Glipizide (52 weeks)</b>	<b>N=408</b>	–	<b>N=406</b>
Major [n (%)]	3 (0.7)	–	0
Minor [n (%)]	147 (36.0)	–	7 (1.7)
<b>Add-on to Glimepiride* (24 weeks)</b>	<b>N=146</b>	<b>N=145</b>	<b>N=151</b>
Major [n (%)]	0	0	0
Minor [n (%)]	3 (2.1)	8 (5.5)	9 (6.0)
<b>Add-on to Metformin and a Sulfonylurea (24 weeks)</b>	<b>N=109</b>	–	<b>N=109</b>
Major [n (%)]	0	–	0
Minor [n (%)]	4 (3.7)	–	14 (12.8)
<b>Add-on to Pioglitazone* (24 weeks)</b>	<b>N=139</b>	<b>N=141</b>	<b>N=140</b>
Major [n (%)]	0	0	0
Minor [n (%)]	0	3 (2.1)	0
<b>Add-on to DPP4 inhibitor (24 weeks)</b>	<b>N=226</b>	–	<b>N=225</b>
Major [n (%)]	0	–	1 (0.4)
Minor [n (%)]	3 (1.3)	–	4 (1.8)
<b>Add-on to Insulin with or without other OADs<sup>‡</sup></b>	<b>N=197</b>	<b>N=212</b>	<b>N=196</b>

Major [n (%)]	1 (0.5)	1 (0.5)	1 (0.5)
Minor [n (%)]	67 (34.0)	92 (43.4)	79 (40.3)

\* Major episodes of hypoglycemia were defined as symptomatic episodes requiring external (third party) assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value <54 mg/dL and prompt recovery after glucose or glucagon administration.

† Minor episodes of hypoglycemia were defined as either a symptomatic episode with a capillary or plasma glucose measurement <63 mg/dL regardless of need for external assistance, or an asymptomatic capillary or plasma glucose measurement <63 mg/dL that does not qualify as a major episode.

‡ OAD = oral antidiabetic therapy

## Genital Mycotic Infections

Genital mycotic infections were more frequent with Forxiga treatment. Genital mycotic infections were reported in 0.9% of patients on placebo, 5.7% on Forxiga 5 mg, and 4.8% on Forxiga 10 mg, in the 12-study placebo-controlled pool. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with Forxiga 10 mg. Infections were more frequently reported in females than in males (see Table 1). The most frequently reported genital mycotic infections were vulvovaginal mycotic infections in females and balanitis in males. Patients with a history of genital mycotic infections were more likely to have a genital mycotic infection during the study than those with no prior history (10.0%, 23.1%, and 25.0% versus 0.8%, 5.9%, and 5.0% on placebo, Forxiga 5 mg, and Forxiga 10 mg, respectively).

## Hypersensitivity Reactions

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

## Laboratory Tests

### *Increase in 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 from baseline in hematocrit were -0.33% in the placebo group and 2.30% in the Forxiga 10 mg group. By Week 24, hematocrit values >55% were reported in 0.4% of placebo-treated patients and 1.3% of Forxiga 10 mg-treated patients.

### ***Increase in Serum Inorganic Phosphorus***

In the pool of 13 placebo-controlled studies, increases from baseline in mean serum phosphorus levels were reported at Week 24 in Forxiga-treated patients compared with placebo-treated patients (mean increase of 0.13 versus -0.04 mg/dL, respectively). Higher proportions of patients with marked laboratory abnormalities of hyperphosphatemia ( $\geq 5.6$  mg/dL for age 17-65 years or  $\geq 5.1$  mg/dL for age  $\geq 66$  years) were reported on Forxiga at Week 24 (0.9% versus 1.7% for placebo and Forxiga 10 mg, respectively).

### ***Increase in Low-Density Lipoprotein Cholesterol***

In the pool of 13 placebo-controlled studies, changes from baseline in mean lipid values were reported in Forxiga-treated patients compared to placebo-treated patients. Mean percent changes from baseline at Week 24, were 0.0% versus 2.5% for total cholesterol and -1.0% versus 2.9% for LDL cholesterol, in the placebo and Forxiga 10 mg groups, respectively.

### ***Decrease in Serum Bicarbonate***

In a study of concomitant therapy of Forxiga 10 mg with exenatide extended-release (on a background of metformin), four patients (1.7%) on concomitant therapy had a serum bicarbonate value of less than or equal to 13 mEq/L compared to one each (0.4%) in the Forxiga and exenatide-extended release treatment groups [see *Warnings and Precautions* (5.2)].

## **6.2 Postmarketing Experience**

Additional adverse reactions have been identified during postapproval use of Forxiga. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Ketoacidosis [see *Warnings and Precautions* (5.2)]
- Acute Kidney Injury and Impairment in Renal Function [see *Warnings and Precautions* (5.3)]
- Urosepsis and Pyelonephritis [see *Warnings and Precautions* (5.4)]
- Rash

## **7 DRUG INTERACTIONS**

### **7.1 Positive Urine Glucose Test**

Monitoring glycemic control with urine glucose tests is not recommended in patients taking

SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

## **7.2 Interference with 1,5-anhydroglucitol (1,5-AG) Assay**

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

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### ***Risk Summary***

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

Limited data with Forxiga in pregnant women are not sufficient to determine drug associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy [see *Clinical Considerations*].

In animal studies, adverse renal pelvic and tubule dilatations, that were not fully reversible, were observed in rats when dapagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy, at all doses tested; the lowest of which provided an exposure 15-times the 10 mg clinical dose [see *Data*].

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c greater than 7% and has been reported to be as high as 20 to 25% in women with HbA1c greater than 10%. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

#### ***Clinical Considerations***

*Disease associated maternal and/or embryo-fetal risk*

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, still birth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

## **Data**

### *Animal Data*

Dapagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg/kg/day, increased kidney weights and increased the incidence of renal pelvic and tubular dilatations at all dose levels. Exposure at the lowest dose tested was 15-times the 10 mg clinical dose (based on AUC). The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within a 1-month recovery period.

In a prenatal and postnatal development study, dapagliflozin was administered to maternal rats from gestation day 6 through lactation day 21 at doses of 1, 15, or 75 mg/kg/day, and pups were indirectly exposed *in utero* and throughout lactation. Increased incidence or severity of renal pelvic dilatation was observed in 21-day-old pups offspring of treated dams at 75 mg/kg/day (maternal and pup dapagliflozin exposures were 1415-times and 137-times, respectively, the human values at the 10 mg clinical dose, based on AUC). Dose-related reductions in pup body weights were observed at greater or equal to 29-times the 10 mg clinical dose (based on AUC). No adverse effects on developmental endpoints were noted at 1 mg/kg/day (19-times the 10 mg clinical dose, based on AUC).

In embryo-fetal development studies in rats and rabbits, dapagliflozin was administered throughout organogenesis, corresponding to the first trimester of human pregnancy. In rats, dapagliflozin was neither embryo-lethal nor teratogenic at doses greater than 75 mg/kg/day (1441-times the 10mg clinical dose, based on AUC). Dose related effects on the rat fetus (structural abnormalities and reduced body weight) occurred only at higher dosages, greater than 150 mg/kg (more than 2344-times the 10 mg clinical dose, based on AUC), which were associated with maternal toxicity. These outcomes occurred with drug exposure during periods of renal development in rats that corresponds to the late second and third trimester of human development. No developmental toxicities were observed in rabbits at doses up to 180 mg/kg/day (1191-times the 10 mg clinical dose, based on AUC).

## **8.2 Lactation**

### **Risk Summary**

There is no information regarding the presence of dapagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Dapagliflozin is present in the milk of lactating rats [see *Data*]. However, due to species specific differences in lactation physiology, the clinical relevance of these data are not clear. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because of the potential for serious adverse reactions in breastfed infants, advise women that use of Forxiga is not recommended while breastfeeding.

### **Data**

It is not known whether Forxiga is excreted in human milk. Dapagliflozin was present in rat milk at a milk/plasma ratio of 0.49 indicating that dapagliflozin and its metabolites are transferred into milk at a concentration that is approximately 50% of that in maternal plasma. Juvenile rats directly exposed to dapagliflozin showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

## **8.4 Pediatric Use**

Safety and effectiveness of Forxiga in pediatric patients under 18 years of age have not been established.

## **8.5 Geriatric Use**

No Forxiga dosage change is recommended based on age. A total of 1424 (24%) of the 5936 Forxiga-treated patients were 65 years and older and 207 (3.5%) patients were 75 years and older in a pool of 21 double-blind, controlled, clinical safety and efficacy studies of Forxiga. After controlling for level of renal function (eGFR), efficacy was similar for patients under age 65 years and those 65 years and older. In patients  $\geq 65$  years of age, a higher proportion of patients treated with Forxiga had adverse reactions related to volume depletion and renal impairment or failure compared to patients treated with placebo [see *Warnings and Precautions (5.1)* and *Adverse Reactions (6.1)*].

## **8.6 Renal Impairment**

The safety and efficacy of Forxiga were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m<sup>2</sup>). Compared to placebo-treated patients, patients with moderate renal impairment treated with Forxiga did not have improvement in glycemic control [see *Clinical Studies (14.7)*] and had more renal-related adverse reactions and

more bone fractures [see *Dosage and Administration (2.2)*, *Warnings and Precautions (5.3)*, and *Adverse Reactions (6.1)*]; therefore, Forxiga should not be initiated in this population.

Based on its mechanism of action, Forxiga is not expected to be effective in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m<sup>2</sup>) or ESRD [see *Contraindications (4)*].

## 8.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild, moderate, or 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 [see *Clinical Pharmacology (12.3)*].

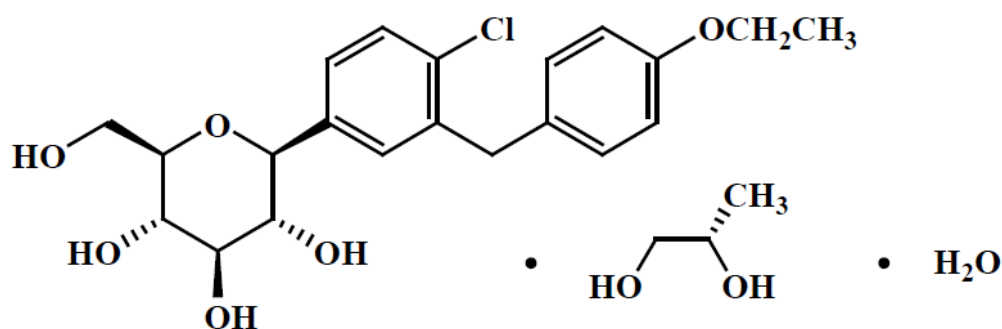
## 10 OVERDOSAGE

There were no reports of overdose during the clinical development program for Forxiga.

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ supportive measures, as dictated by the patient's clinical status. The removal of dapagliflozin by hemodialysis has not been studied.

## 11 DESCRIPTION

Dapagliflozin 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<sub>21</sub>H<sub>25</sub>ClO<sub>6</sub>•C<sub>3</sub>H<sub>8</sub>O<sub>2</sub>•H<sub>2</sub>O and the molecular weight is 502.98. The structural formula is:



Forxiga is available as a film-coated tablet for oral administration containing the equivalent of

5 mg dapagliflozin as dapagliflozin propanediol or the equivalent of 10 mg dapagliflozin as dapagliflozin propanediol, 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.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

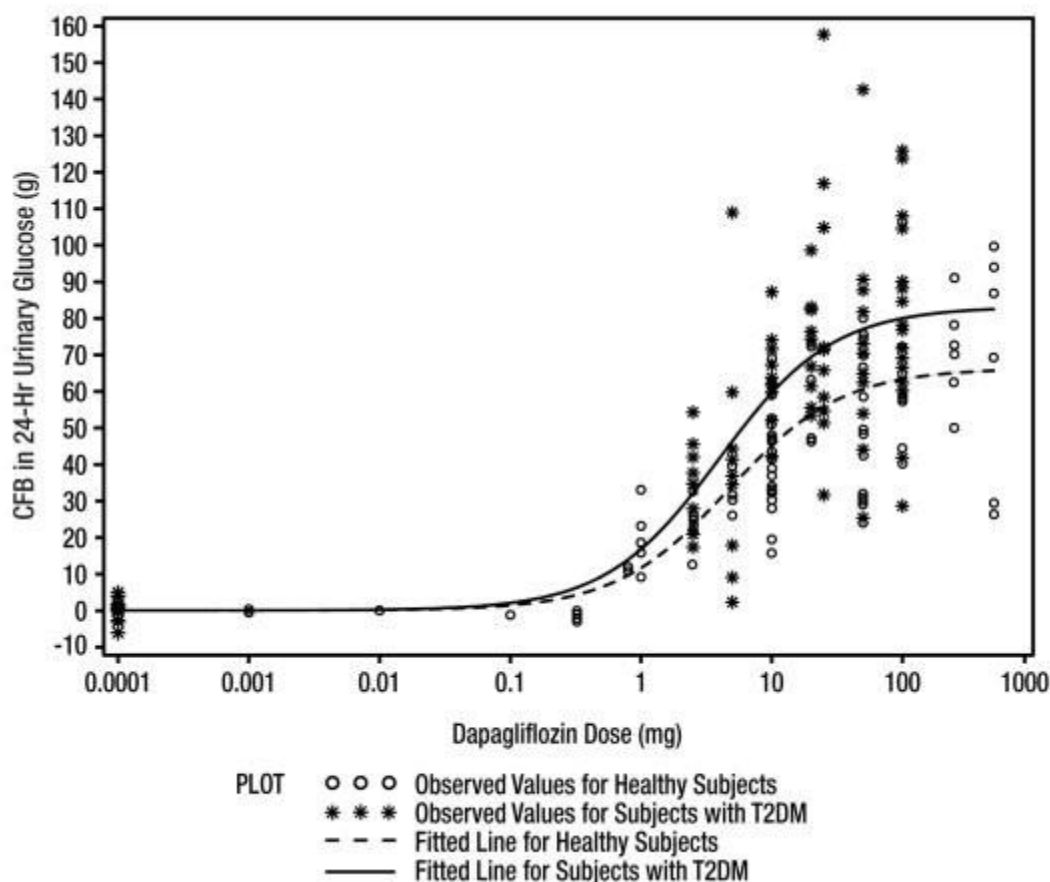
### **12.2 Pharmacodynamics**

#### **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). Dapagliflozin doses of 5 or 10 mg per day in patients with type 2 diabetes mellitus for 12 weeks resulted in excretion of approximately 70 grams of glucose in the urine per day at Week 12. A near maximum glucose excretion was observed at the dapagliflozin daily dose of 20 mg. This urinary glucose excretion with dapagliflozin also results in increases in urinary volume [see *Adverse Reactions (6.1)*].



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



## Cardiac Electrophysiology

Dapagliflozin was not associated with clinically meaningful prolongation of QTc interval at daily doses up to 150 mg (15 times the recommended maximum 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 maximum dose) of dapagliflozin in healthy subjects.

## 12.3 Pharmacokinetics

### Absorption

Following oral administration of dapagliflozin, the maximum plasma concentration ( $C_{max}$ ) is usually attained within 2 hours under fasting state. The  $C_{max}$  and AUC values increase dose proportionally with increase in dapagliflozin dose in the therapeutic dose range. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%.

Administration of dapagliflozin with a high-fat meal decreases its  $C_{\max}$  by up to 50% and prolongs  $T_{\max}$  by approximately 1 hour, but does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful and dapagliflozin can be administered with or without food.

## **Distribution**

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

## **Metabolism**

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

## **Elimination**

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [14C]-dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively. In urine, less than 2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life ( $t_{1/2}$ ) for dapagliflozin is approximately 12.9 hours following a single oral dose of Forxiga 10 mg.

## **Specific Populations**

### ***Renal Impairment***

At steady state (20 mg once-daily dapagliflozin for 7 days), patients with type 2 diabetes with mild, moderate, or severe renal impairment (as determined by eGFR) had geometric mean systemic exposures of dapagliflozin that were 45%, 2.04-fold, and 3.03-fold higher, respectively, as compared to patients with type 2 diabetes with normal renal function. Higher systemic exposure of dapagliflozin in patients with type 2 diabetes mellitus with renal impairment did not result in a correspondingly higher 24-hour urinary glucose excretion. The steady-state 24-hour urinary glucose excretion in patients with type 2 diabetes and mild, moderate, and severe renal impairment was 42%, 80%, and 90% lower, respectively, than patients with type 2 diabetes with

normal renal function. The impact of hemodialysis on dapagliflozin exposure is not known. [See *Dosage and Administration (2.2)*, *Warnings and Precautions (5.3)*, *Use in Specific Populations (8.6)*, and *Clinical Studies (14.7)*.]

### ***Hepatic Impairment***

In subjects with mild and moderate hepatic impairment (Child-Pugh classes A and B), mean  $C_{max}$  and AUC of dapagliflozin were up to 12% and 36% higher, respectively, as compared to healthy matched control subjects following single-dose administration of 10 mg dapagliflozin. These differences were not considered to be clinically meaningful. In patients with severe hepatic impairment (Child-Pugh class C), mean  $C_{max}$  and AUC of dapagliflozin were up to 40% and 67% higher, respectively, as compared to healthy matched controls [see *Use in Specific Populations (8.7)*].

### ***Effects of Age, Gender, Race, and Body Weight on Pharmacokinetics***

Based on a population pharmacokinetic analysis, age, gender, race, and body weight do not have a clinically meaningful effect on the pharmacokinetics of dapagliflozin and thus, no dose adjustment is recommended.

### ***Pediatric***

Pharmacokinetics in the pediatric population has not been studied.

### ***Drug Interactions***

#### ***In Vitro Assessment of Drug Interactions***

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

#### ***Effects of Other Drugs on Dapagliflozin***

Table 6 shows the effect of coadministered drugs on the pharmacokinetics of dapagliflozin. No dose adjustments are recommended for dapagliflozin.

**Table 6: Effects of Coadministered Drugs on Dapagliflozin Systemic Exposure**

Coadministered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Effect on Dapagliflozin Exposure (% Change [90% CI])	
		C <sub>max</sub>	AUC <sup>†</sup>
<b>No dosing adjustments required for the following:</b>			
<b>Oral Antidiabetic Agents</b>			
Metformin (1000 mg)	20 mg	↔	↔
Pioglitazone (45 mg)	50 mg	↔	↔
Sitagliptin (100 mg)	20 mg	↔	↔
Glimepiride (4 mg)	20 mg	↔	↔
Voglibose (0.2 mg three times daily)	10 mg	↔	↔
<b>Other Medications</b>			
Hydrochlorothiazide (25 mg)	50 mg	↔	↔
Bumetanide (1 mg)	10 mg once daily for 7 days	↔	↔
Valsartan (320 mg)	20 mg	↓12% [↓3%, ↓20%]	↔
Simvastatin (40 mg)	20 mg	↔	↔
<b>Anti-infective Agent</b>			
Rifampin (600 mg once daily for 6 days)	10 mg	↓7% [↓22%, ↑11%]	↓22% [↓27%, ↓17%]
<b>Nonsteroidal Anti-inflammatory Agent</b>			
Mefenamic Acid (loading dose of 500 mg followed by 14 doses of 250 mg every 6 hours)	10 mg	↑13% [↑3%, ↑24%]	↑51% [↑44%, ↑58%]

\* Single dose unless otherwise noted.

<sup>†</sup> AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses.

↔ = no change (geometric mean ratio of test:reference within 0.80 to 1.25); ↓ or ↑ = parameter was lower or higher, respectively, with coadministration compared to dapagliflozin administered alone (geometric mean ratio of test:reference was lower than 0.80 or higher than 1.25).

### Effects of Dapagliflozin on Other Drugs

Table 7 shows the effect of dapagliflozin on other coadministered drugs. Dapagliflozin did not meaningfully affect the pharmacokinetics of the coadministered drugs.

**Table 7: Effects of Dapagliflozin on the Systemic Exposures of Coadministered Drugs**

Coadministered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Effect on Coadministered Drug Exposure (% Change [90% CI])	
		C <sub>max</sub>	AUC <sup>†</sup>
<b>No dosing adjustments required for the following:</b>			
<b>Oral Antidiabetic Agents</b>			
Metformin (1000 mg)	20 mg	↔	↔
Pioglitazone (45 mg)	50 mg	↓7% [↓25%, ↑15%]	↔

Sitagliptin (100 mg)	20 mg	↔	↔
Glimepiride (4 mg)	20 mg	↔	↑13% [0%, ↑29%]
<b>Other Medications</b>			
Hydrochlorothiazide (25 mg)	50 mg	↔	↔
Bumetanide (1 mg)	10 mg once daily for 7 days	↑13% [↓2%, ↑31%]	↑13% [↓1%, ↑30%]
Valsartan (320 mg)	20 mg	↓6% [↓24%, ↑16%]	↑5% [↓15%, ↑29%]
Simvastatin (40 mg)	20 mg	↔	↑19%
Digoxin (0.25 mg)	20 mg loading dose then 10 mg once daily for 7 days	↔	↔
Warfarin (25 mg)	20 mg loading dose then 10 mg once daily for 7 days	↔	↔

\* Single dose unless otherwise noted.

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

↔ = no change (geometric mean ratio of test:reference within 0.80 to 1.25); ↓ or ↑ = parameter was lower or higher, respectively, with coadministration compared to dapagliflozin administered alone (geometric mean ratio of test:reference was lower than 0.80 or higher than 1.25).

## 13 NONCLINICAL TOXICOLOGY

### 13.1 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 approximately 72 times (males) and 105 times (females) the clinical dose of 10 mg per day based on AUC exposure. In rats, the highest dose was approximately 131 times (males) and 186 times (females) the clinical dose of 10 mg per day based on AUC exposure.

Dapagliflozin was negative in the Ames mutagenicity assay and was positive in a series of *in vitro* clastogenicity assays in the presence of S9 activation and at concentrations  $\geq 100$   $\mu\text{g/mL}$ . Dapagliflozin was negative for clastogenicity in a series of *in vivo* studies evaluating micronuclei or DNA repair in rats at exposure multiples  $>2100$  times the clinical dose.

There was no carcinogenicity or mutagenicity signal in animal studies, suggesting that dapagliflozin does not represent a genotoxic risk to humans.

Dapagliflozin had no effects on mating, fertility, or early embryonic development in treated male or female rats at exposure multiples  $\leq 1708$  times and 998 times the maximum recommended

human dose in males and females, respectively.

## 14 CLINICAL STUDIES

### 14.1 Overview of Clinical Studies of Forxiga for Type 2 Diabetes

Forxiga has been studied as monotherapy, in combination with metformin, pioglitazone, sulfonyleurea (glimepiride), sitagliptin (with or without metformin), metformin plus a sulfonyleurea, or insulin (with or without other oral antidiabetic therapy), compared to a sulfonyleurea (glipizide), and in combination with a GLP-1 receptor agonist (exenatide extended-release) added-on to metformin. Forxiga has also been studied in patients with type 2 diabetes and moderate renal impairment.

Treatment with Forxiga as monotherapy and in combination with metformin, glimepiride, pioglitazone, sitagliptin, or insulin produced statistically significant improvements in mean change from baseline at Week 24 in HbA1c compared to control. Reductions in HbA1c were seen across subgroups including gender, age, race, duration of disease, and baseline BMI.

### 14.2 Monotherapy

A total of 840 treatment-naive patients with inadequately controlled type 2 diabetes participated in 2 placebo-controlled studies to evaluate the safety and efficacy of monotherapy with Forxiga.

In 1 monotherapy study, a total of 558 treatment-naive patients with inadequately controlled diabetes participated in a 24-week study. Following a 2-week diet and exercise placebo lead-in period, 485 patients with HbA1c  $\geq 7\%$  and  $\leq 10\%$  were randomized to Forxiga 5 mg or Forxiga 10 mg once daily in either the morning (QAM, main cohort) or evening (QPM), or placebo.

At Week 24, treatment with Forxiga 10 mg QAM provided significant improvements in HbA1c and FPG compared with placebo (see Table 8).

**Table 8: Results at Week 24 (LOCF\*) in a Placebo-Controlled Study of Forxiga Monotherapy in Patients with Type 2 Diabetes (Main Cohort AM Doses)**

Efficacy Parameter	Forxiga 10 mg N=70 <sup>†</sup>	Forxiga 5 mg N=64 <sup>†</sup>	Placebo N=75 <sup>†</sup>
<b>HbA1c (%)</b>			
Baseline (mean)	8.0	7.8	7.8
Change from baseline (adjusted mean <sup>‡</sup> )	-0.9	-0.8	-0.2
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-0.7 <sup>§</sup> (-1.0, -0.4)	-0.5 (-0.8, -0.2)	

Percent of patients achieving HbA1c <7% adjusted for baseline	50.8% <sup>¶</sup>	44.2% <sup>¶</sup>	31.6%
<b>FPG (mg/dL)</b>			
Baseline (mean)	166.6	157.2	159.9
Change from baseline (adjusted mean <sup>‡</sup> )	-28.8	-24.1	-4.1
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-24.7 <sup>§</sup> (-35.7, -13.6)	-19.9 (-31.3, -8.5)	

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

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

‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001 versus placebo. Sensitivity analyses yielded smaller estimates of treatment difference with placebo.

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

### 14.3 Initial Combination Therapy with Metformin XR

A total of 1241 treatment-naïve patients with inadequately controlled type 2 diabetes (HbA1c  $\geq 7.5\%$  and  $\leq 12\%$ ) participated in 2 active-controlled studies of 24-week duration to evaluate initial therapy with Forxiga 5 mg or 10 mg in combination with metformin extended-release (XR) formulation.

In 1 study, 638 patients were randomized to 1 of 3 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 statistically significant improvements in HbA1c and FPG compared with either of the monotherapy treatments and statistically significant reduction in body weight compared with metformin XR alone (see Table 9 and Figure 2). Forxiga 10 mg as monotherapy also provided statistically significant improvements in FPG and statistically significant reduction in body weight compared with metformin alone and was noninferior to metformin XR monotherapy in lowering HbA1c.

**Table 9: 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 <sup>†</sup>	Forxiga 10 mg N=219 <sup>†</sup>	Metformin XR N=208 <sup>†</sup>
<b>HbA1c (%)</b>			
Baseline (mean)	9.1	9.0	9.0

Change from baseline (adjusted mean <sup>‡</sup> )	-2.0	-1.5	-1.4
Difference from Forxiga (adjusted mean <sup>‡</sup> ) (95% CI)	-0.5 <sup>§</sup> (-0.7, -0.3)		
Difference from metformin XR (adjusted mean <sup>‡</sup> ) (95% CI)	-0.5 <sup>§</sup> (-0.8, -0.3)	0.0 <sup>¶</sup> (-0.2, 0.2)	
Percent of patients achieving HbA1c <7% adjusted for baseline	46.6% <sup>#</sup>	31.7%	35.2%
<b>FPG (mg/dL)</b>			
Baseline (mean)	189.6	197.5	189.9
Change from baseline (adjusted mean <sup>‡</sup> )	-60.4	-46.4	-34.8
Difference from Forxiga (adjusted mean <sup>‡</sup> ) (95% CI)	-13.9 <sup>§</sup> (-20.9, -7.0)		
Difference from metformin XR (adjusted mean <sup>‡</sup> ) (95% CI)	-25.5 <sup>§</sup> (-32.6, -18.5)	-11.6 <sup>#</sup> (-18.6, -4.6)	
<b>Body Weight (kg)</b>			
Baseline (mean)	88.6	88.5	87.2
Change from baseline (adjusted mean <sup>‡</sup> )	-3.3	-2.7	-1.4
Difference from metformin XR (adjusted mean <sup>‡</sup> ) (95% CI)	-2.0 <sup>§</sup> (-2.6, -1.3)	-1.4 <sup>§</sup> (-2.0, -0.7)	

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

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

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

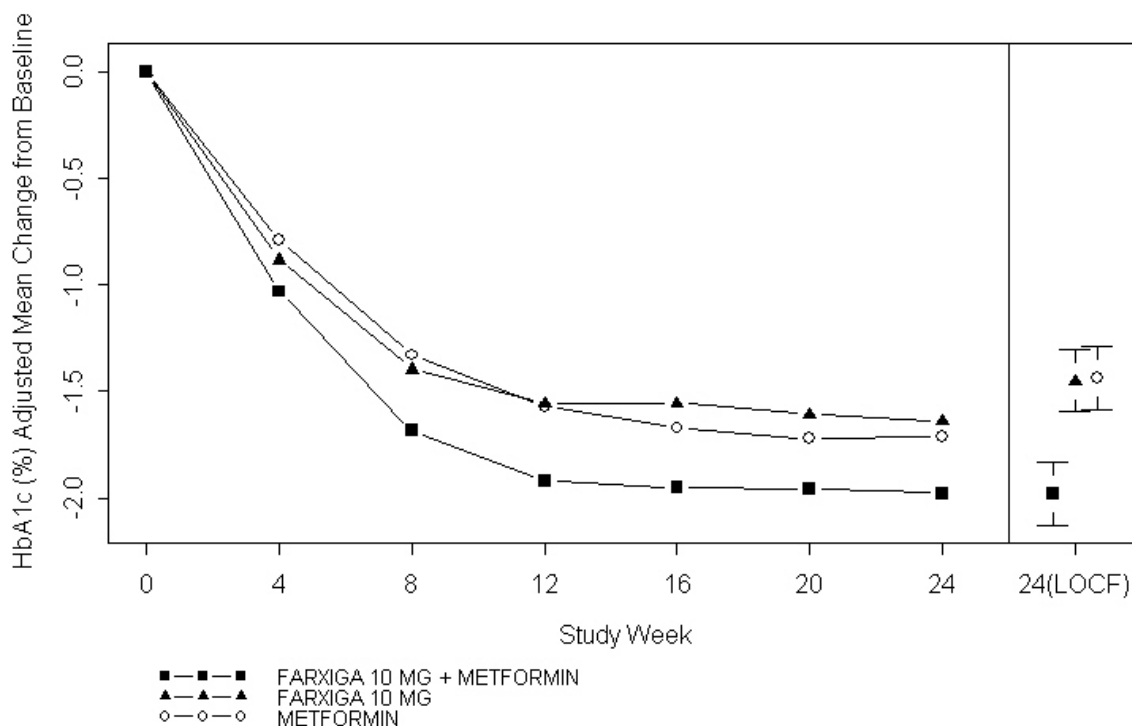
<sup>§</sup> p-value <0.0001.

<sup>¶</sup> Noninferior versus metformin XR.

<sup>#</sup> p-value <0.05.



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



Left side graph: Values for adjusted mean change from baseline based on a longitudinal repeated measures model, including randomized subjects who completed the study with both baseline and Week 24 HbA1c values without rescue.  
 Right side graph for Week 24 (LOCF): Values for adjusted mean change from baseline and 95% CIs based on an ANCOVA model, including randomized subjects with a baseline and at least one post baseline HbA1c before rescue.

In a second study, 603 patients were randomized to 1 of 3 treatment arms following a 1-week lead-in period: Forxiga 5 mg plus metformin XR (up to 2000 mg per day), Forxiga 5 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 5 mg plus metformin XR provided statistically significant improvements in HbA1c and FPG compared with either of the monotherapy treatments and statistically significant reduction in body weight compared with metformin XR alone (see Table 10).

**Table 10: Results at Week 24 (LOCF\*) in an Active-Controlled Study of Forxiga Initial Combination Therapy with Metformin XR**

Efficacy Parameter	Forxiga 5 mg + Metformin XR N=194†	Forxiga 5 mg N=203†	Metformin XR N=201†
HbA1c (%)			

Baseline (mean)	9.2	9.1	9.1
Change from baseline (adjusted mean <sup>†</sup> )	-2.1	-1.2	-1.4
Difference from Forxiga (adjusted mean <sup>†</sup> ) (95% CI)	-0.9 <sup>§</sup> (-1.1, -0.6)		
Difference from metformin XR (adjusted mean <sup>†</sup> ) (95% CI)	-0.7 <sup>§</sup> (-0.9, -0.5)		
Percent of patients achieving HbA1c <7% adjusted for baseline	52.4% <sup>¶</sup>	22.5%	34.6%
<b>FPG (mg/dL)</b>			
Baseline (mean)	193.4	190.8	196.7
Change from baseline (adjusted mean <sup>†</sup> )	-61.0	-42.0	-33.6
Difference from Forxiga (adjusted mean <sup>†</sup> ) (95% CI)	-19.1 <sup>§</sup> (-26.7, -11.4)		
Difference from metformin XR (adjusted mean <sup>†</sup> ) (95% CI)	-27.5 <sup>§</sup> (-35.1, -19.8)		
<b>Body Weight (kg)</b>			
Baseline (mean)	84.2	86.2	85.8
Change from baseline (adjusted mean <sup>†</sup> )	-2.7	-2.6	-1.3
Difference from metformin XR (adjusted mean <sup>†</sup> ) (95% CI)	-1.4 <sup>§</sup> (-2.0, -0.7)		

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

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

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

<sup>§</sup> p-value <0.0001.

<sup>¶</sup> p-value <0.05.

## 14.4 Add-On to Metformin

A total of 546 patients with type 2 diabetes with inadequate glycemic control (HbA1c  $\geq 7\%$  and  $\leq 10\%$ ) participated in a 24-week, placebo-controlled study 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 Forxiga 5 mg, Forxiga 10 mg, or placebo in addition to their current dose of metformin.

As add-on treatment to metformin, Forxiga 10 mg provided statistically significant improvements in HbA1c and FPG, and statistically significant reduction in body weight compared with placebo at Week 24 (see Table 11 and Figure 3). Statistically significant ( $p < 0.05$  for both doses) mean changes from baseline in systolic blood pressure relative to placebo plus metformin were -4.5 mmHg and -5.3 mmHg with Forxiga 5 mg and 10 mg plus metformin, respectively.

**Table 11: Results of a 24-Week (LOCF\*) Placebo-Controlled Study of**

**Forxiga in Add-On Combination with Metformin**

<b>Efficacy Parameter</b>	<b>Forxiga 10 mg + Metformin N=135<sup>†</sup></b>	<b>Forxiga 5 mg + Metformin N=137<sup>†</sup></b>	<b>Placebo + Metformin N=137<sup>†</sup></b>
<b>HbA1c (%)</b>			
Baseline (mean)	7.9	8.2	8.1
Change from baseline (adjusted mean <sup>‡</sup> )	-0.8	-0.7	-0.3
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-0.5 <sup>§</sup> (-0.7, -0.3)	-0.4 <sup>§</sup> (-0.6, -0.2)	
Percent of patients achieving HbA1c <7% adjusted for baseline	40.6% <sup>¶</sup>	37.5% <sup>¶</sup>	25.9%
<b>FPG (mg/dL)</b>			
Baseline (mean)	156.0	169.2	165.6
Change from baseline at Week 24 (adjusted mean <sup>‡</sup> )	-23.5	-21.5	-6.0
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-17.5 <sup>§</sup> (-25.0, -10.0)	-15.5 <sup>§</sup> (-22.9, -8.1)	
Change from baseline at Week 1 (adjusted mean <sup>‡</sup> )	-16.5 <sup>§</sup> (N=115)	-12.0 <sup>§</sup> (N=121)	1.2 (N=126)
<b>Body Weight (kg)</b>			
Baseline (mean)	86.3	84.7	87.7
Change from baseline (adjusted mean <sup>‡</sup> )	-2.9	-3.0	-0.9
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-2.0 <sup>§</sup> (-2.6, -1.3)	-2.2 <sup>§</sup> (-2.8, -1.5)	

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

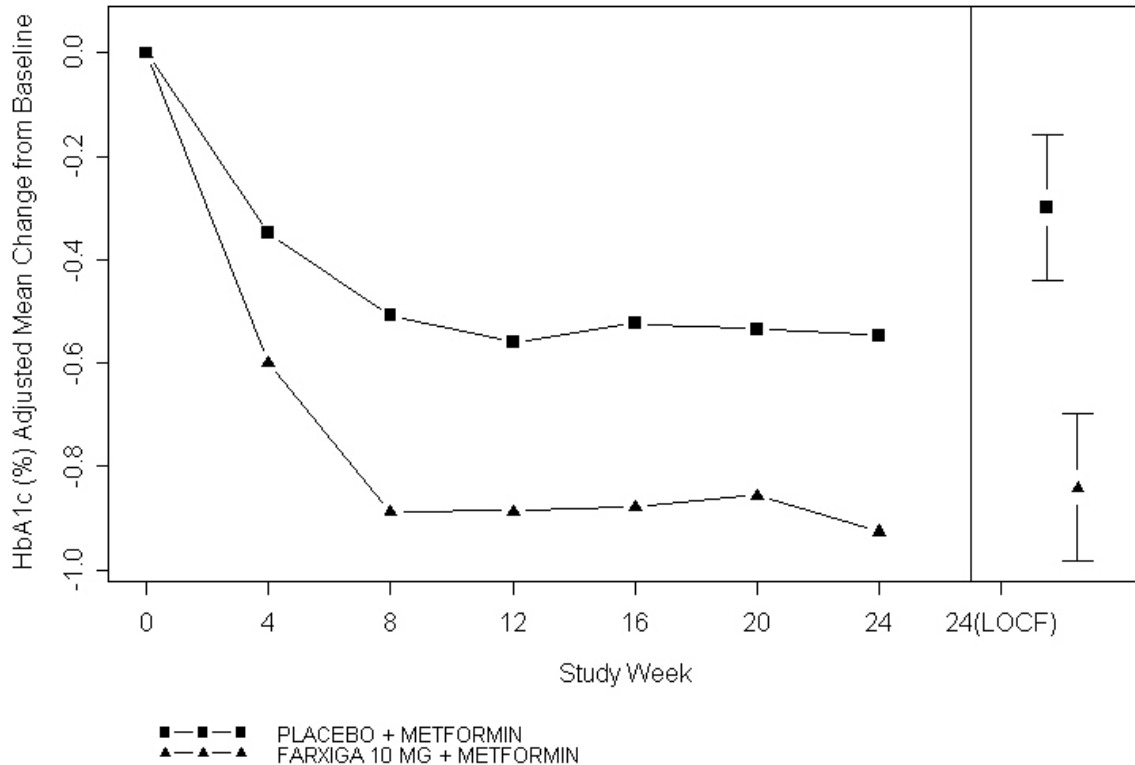
<sup>†</sup> All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.

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

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

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

**Figure 3: Adjusted Mean Change from Baseline Over Time in HbA1c (%) in a 24-Week Placebo-Controlled Study of Forxiga in Combination with Metformin**



Left side graph: Values for adjusted mean change from baseline based on a longitudinal repeated measures model, including randomized subjects who completed Short-Term Period with both baseline and Week 24 HbA1c values without rescue.  
 Right side graph for Week 24 (LOCF): Values for adjusted mean change from baseline and 95% CIs based on an ANCOVA model, including randomized subjects with a baseline and at least one post baseline HbA1c before rescue.

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

At the end of the titration period, 87% of patients treated with Forxiga had been titrated to the maximum study dose (10 mg) versus 73% treated with glipizide (20 mg). Forxiga led to a similar mean reduction in HbA1c from baseline at Week 52 (LOCF), compared with glipizide,

thus demonstrating noninferiority (see Table 12). Forxiga treatment led to a statistically significant mean reduction in body weight from baseline at Week 52 (LOCF) compared with a mean increase in body weight in the glipizide group. Statistically significant ( $p < 0.0001$ ) mean change from baseline in systolic blood pressure relative to glipizide plus metformin was  $-5.0$  mmHg with Forxiga plus metformin.

**Table 12: Results at Week 52 (LOCF\*) in an Active-Controlled Study Comparing Forxiga to Glipizide as Add-On to Metformin**

Efficacy Parameter	Forxiga + Metformin N=400 <sup>†</sup>	Glipizide + Metformin N=401 <sup>†</sup>
<b>HbA1c (%)</b>		
Baseline (mean)	7.7	7.7
Change from baseline (adjusted mean <sup>‡</sup> )	-0.5	-0.5
Difference from glipizide + metformin (adjusted mean <sup>‡</sup> ) (95% CI)	0.0 <sup>§</sup> (-0.1, 0.1)	
<b>Body Weight (kg)</b>		
Baseline (mean)	88.4	87.6
Change from baseline (adjusted mean <sup>‡</sup> )	-3.2	1.4
Difference from glipizide + metformin (adjusted mean <sup>‡</sup> ) (95% CI)	-4.7 <sup>¶</sup> (-5.1, -4.2)	

\* LOCF: last observation carried forward.

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

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

<sup>§</sup> Noninferior to glipizide + metformin.

<sup>¶</sup> p-value  $< 0.0001$ .

## 14.6 Add-On Combination Therapy with Other Antidiabetic Agents

### Add-On Combination Therapy with a Sulfonylurea

A total of 597 patients with type 2 diabetes and inadequate glycemic control ( $\text{HbA1c} \geq 7\%$  and  $\leq 10\%$ ) were randomized in this 24-week, placebo-controlled study to evaluate Forxiga in combination with glimepiride (a sulfonylurea).

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

In combination with glimepiride, Forxiga 10 mg provided statistically significant improvement in HbA1c, FPG, and 2-hour PPG, and statistically significant reduction in body weight compared with placebo plus glimepiride at Week 24 (see Table 13). Statistically

significant ( $p < 0.05$  for both doses) mean changes from baseline in systolic blood pressure relative to placebo plus glimepiride were  $-2.8$  mmHg and  $-3.8$  mmHg with Forxiga 5 mg and 10 mg plus glimepiride, respectively.

### **Add-on Combination Therapy with Metformin and a Sulfonylurea**

A total of 218 patients with type 2 diabetes and inadequate glycemic control ( $HbA1c \geq 7\%$  and  $\leq 10.5\%$ ) participated in a 24-week, placebo-controlled study to evaluate Forxiga in combination with metformin and a sulfonylurea. Patients on a stable dose of metformin (immediate- or extended-release formulations)  $\geq 1500$  mg/day plus maximum tolerated dose, which must be at least half the maximum dose, of a sulfonylurea for at least 8 weeks prior to enrollment were randomized after an 8-week placebo lead-in period to Forxiga 10 mg or placebo. Dose-titration of Forxiga or metformin was not permitted during the 24-week treatment period. Down-titration of the sulfonylurea was permitted to prevent hypoglycemia, but no up-titration was permitted. As add-on treatment to combined metformin and a sulfonylurea, treatment with Forxiga 10 mg provided statistically significant improvements in HbA1c and FPG and statistically significant reduction in body weight compared with placebo at Week 24 (Table 13). A statistically significant ( $p < 0.05$ ) mean change from baseline in systolic blood pressure relative to placebo in combination with metformin and a sulfonylurea was  $-3.8$  mmHg with Forxiga 10 mg in combination with metformin and a sulfonylurea at Week 8.

### **Add-On Combination Therapy with a Thiazolidinedione**

A total of 420 patients with type 2 diabetes with inadequate glycemic control ( $HbA1c \geq 7\%$  and  $\leq 10.5\%$ ) participated in a 24-week, placebo-controlled study to evaluate Forxiga in combination with pioglitazone (a thiazolidinedione [TZD]) alone. Patients on a stable dose of pioglitazone of 45 mg per day (or 30 mg per day, if 45 mg per day was not tolerated) for 12 weeks were randomized after a 2-week lead-in period to 5 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 statistically significant improvements in HbA1c, 2-hour PPG, FPG, the proportion of patients achieving  $HbA1c < 7\%$ , and a statistically significant reduction in body weight compared with the placebo plus pioglitazone treatment groups (see Table 13) at Week 24. A statistically significant ( $p < 0.05$ ) mean change from baseline in systolic blood pressure relative to placebo in combination with pioglitazone was  $-4.5$  mmHg with Forxiga 10 mg in combination with pioglitazone.

### **Add-On Combination Therapy with a DPP4 Inhibitor**

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 ( $\text{HbA1c} \geq 7.0\%$  and  $\leq 10.0\%$  at randomization), participated in a 24-week, placebo-controlled study 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 ( $\geq 1500$  mg per day), and within each stratum were randomized to either Forxiga 10 mg plus sitagliptin 100 mg once daily, or placebo plus sitagliptin 100 mg once daily. Endpoints were tested for Forxiga 10 mg versus placebo for the total study group (sitagliptin with and without metformin) and for each stratum (sitagliptin alone or sitagliptin with metformin). Thirty-seven percent (37%) of patients were drug naive, 32% were on metformin alone, 13% were on a DPP4 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 or without metformin), Forxiga 10 mg provided statistically significant improvements in HbA1c, FPG, and a statistically significant reduction in body weight compared with the placebo plus sitagliptin (with or without metformin) group at Week 24 (see Table 13). These improvements were also seen in the stratum of patients who received Forxiga 10 mg plus sitagliptin alone (placebo-corrected mean change for HbA1c  $-0.56\%$ ;  $n=110$ ) compared with placebo plus sitagliptin alone ( $n=111$ ), and the stratum of patients who received Forxiga 10 mg plus sitagliptin and metformin (placebo-corrected mean change for HbA1c  $-0.40$ ;  $n=113$ ) compared with placebo plus sitagliptin with metformin ( $n=113$ ).

### **Add-On Combination Therapy with Insulin**

A total of 808 patients with type 2 diabetes who had inadequate glycemic control ( $\text{HbA1c} \geq 7.5\%$  and  $\leq 10.5\%$ ) were randomized in a 24-week, placebo-controlled study to evaluate Forxiga as add-on therapy to insulin. Patients on a stable insulin regimen, with a mean dose of at least 30 IU of injectable insulin per day, for a period of at least 8 weeks prior to enrollment and on a maximum of 2 oral antidiabetic medications (OADs), including metformin, were randomized after completing a 2-week enrollment period to receive either Forxiga 5 mg, Forxiga 10 mg, or placebo in addition to their current dose of insulin and other OADs, if applicable.

Patients were stratified according to the presence or absence of background OADs. Up- or down-titration of insulin was only permitted during the treatment phase in patients who failed to meet specific glycemic goals. Dose modifications of blinded study medication or OAD(s) were not allowed during the treatment phase, with the exception of decreasing OAD(s) where there were concerns over hypoglycemia after cessation of insulin therapy.

In this study, 50% of patients were on insulin monotherapy at baseline, while 50% were on 1 or 2 OADs in addition to insulin. At Week 24, Forxiga 10 mg dose provided statistically significant improvement in HbA1c and reduction in mean insulin dose, and a statistically significant reduction in body weight compared with placebo in combination with insulin, with or without up to 2 OADs (see Table 13); the effect of Forxiga on HbA1c was similar in patients treated with insulin alone and patients treated with insulin plus OAD. Statistically significant ( $p < 0.05$ ) mean change from baseline in systolic blood pressure relative to placebo in combination with insulin was  $-3.0$  mmHg with Forxiga 10 mg in combination with insulin.

At Week 24, Forxiga 5 mg ( $-5.7$  IU, difference from placebo) and 10 mg ( $-6.2$  IU, difference from placebo) once daily resulted in a statistically significant reduction in mean daily insulin dose ( $p < 0.0001$  for both doses) compared to placebo in combination with insulin, and a statistically significantly higher proportion of patients on Forxiga 10 mg (19.6%) reduced their insulin dose by at least 10% compared to placebo (11.0%).

**Table 13: Results of 24-Week (LOCF\*) Placebo-Controlled Studies of Forxiga in Combination with Antidiabetic Agents**

Efficacy Parameter	Forxiga 10 mg	Forxiga 5 mg	Placebo
<b>In Combination with Sulfonylurea (Glimepiride)</b>			
<b>Intent-to-Treat Population</b>	N=151 <sup>†</sup>	N=142 <sup>†</sup>	N=145 <sup>†</sup>
<b>HbA1c (%)</b>			
Baseline (mean)	8.1	8.1	8.2
Change from baseline (adjusted mean <sup>‡</sup> )	-0.8	-0.6	-0.1
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-0.7 <sup>¶</sup> (-0.9, -0.5)	-0.5 <sup>¶</sup> (-0.7, -0.3)	
Percent of patients achieving HbA1c <7% adjusted for baseline	31.7% <sup>¶</sup>	30.3% <sup>¶</sup>	13.0%
<b>FPG (mg/dL)</b>			
Baseline (mean)	172.4	174.5	172.7
Change from baseline (adjusted mean <sup>‡</sup> )	-28.5	-21.2	-2.0
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-26.5 <sup>¶</sup> (-33.5, -19.5)	-19.3 <sup>¶</sup> (-26.3, -12.2)	
<b>2-hour PPG<sup>#</sup> (mg/dL)</b>			
Baseline (mean)	329.6	322.8	324.1
Change from baseline (adjusted mean <sup>‡</sup> )	-60.6	-54.5	-11.5
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-49.1 <sup>¶</sup> (-64.1, -34.1)	-43.0 <sup>¶</sup> (-58.4, -27.5)	
<b>Body Weight (kg)</b>			
Baseline (mean)	80.6	81.0	80.9
Change from baseline (adjusted mean <sup>‡</sup> )	-2.3	-1.6	-0.7
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-1.5 <sup>¶</sup> (-2.2, -0.9)	-0.8 <sup>¶</sup> (-1.5, -0.2)	
<b>In Combination with Metformin and a Sulfonylurea</b>			



<b>Intent-to-Treat Population</b>	<b>N=108<sup>†</sup></b>	<b>-</b>	<b>N=108<sup>†</sup></b>
<b>HbA1c (%)</b>			
Baseline (mean)	8.08	-	8.24
Change from baseline (adjusted mean <sup>‡§</sup> )	-0.86	-	-0.17
Difference from placebo (adjusted mean <sup>‡§</sup> ) (95% CI)	-0.69 <sup>¶</sup> (-0.89, -0.49)	-	
Percent of patients achieving HbA1c <7% adjusted for baseline	31.8% <sup>¶</sup>	-	11.1%
<b>FPG (mg/dL)</b>			
Baseline (mean)	167.4	-	180.3
Change from baseline (adjusted mean <sup>‡</sup> )	-34.2	-	-0.8
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-33.5 <sup>¶</sup> (-43.1, -23.8)	-	
<b>Body Weight (kg)</b>			
Baseline (mean)	88.57	-	90.07
Change from baseline (adjusted mean <sup>‡</sup> )	-2.65	-	-0.58
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-2.07 <sup>¶</sup> (-2.79, -1.35)	-	
<b>In Combination with Thiazolidinedione (Pioglitazone)</b>			
<b>Intent-to-Treat Population</b>	<b>N=140<sup>**</sup></b>	<b>N=141<sup>**</sup></b>	<b>N=139<sup>**</sup></b>
<b>HbA1c (%)</b>			
Baseline (mean)	8.4	8.4	8.3
Change from baseline (adjusted mean <sup>‡</sup> )	-1.0	-0.8	-0.4
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-0.6 <sup>¶</sup> (-0.8, -0.3)	-0.4 <sup>¶</sup> (-0.6, -0.2)	
Percent of patients achieving HbA1c <7% adjusted for baseline	38.8% <sup>††</sup>	32.5% <sup>††</sup>	22.4%
<b>FPG (mg/dL)</b>			
Baseline (mean)	164.9	168.3	160.7
Change from baseline (adjusted mean <sup>‡</sup> )	-29.6	-24.9	-5.5
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-24.1 <sup>¶</sup> (-32.2, -16.1)	-19.5 <sup>¶</sup> (-27.5, -11.4)	
<b>2-hour PPG<sup>#</sup> (mg/dL)</b>			
Baseline (mean)	308.0	284.8	293.6
Change from baseline (adjusted mean <sup>‡</sup> )	-67.5	-65.1	-14.1
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-53.3 <sup>¶</sup> (-71.1, -35.6)	-51.0 <sup>¶</sup> (-68.7, -33.2)	
<b>Body Weight (kg)</b>			
Baseline (mean)	84.8	87.8	86.4
Change from baseline (adjusted mean <sup>‡</sup> )	-0.1	0.1	1.6
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-1.8 <sup>¶</sup> (-2.6, -1.0)	-1.6 <sup>¶</sup> (-2.3, -0.8)	
<b>In Combination with DPP4 Inhibitor (Sitagliptin) with or without Metformin</b>			
<b>Intent-to-Treat Population</b>	<b>N=223<sup>†</sup></b>	<b>-</b>	<b>N=224<sup>†</sup></b>
<b>HbA1c (%)</b>			
Baseline (mean)	7.90	-	7.97

Change from baseline (adjusted mean <sup>‡</sup> )	-0.45	-	0.04
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-0.48 <sup>¶</sup> (-0.62, -0.34)	-	
Patients with HbA1c decrease $\geq 0.7\%$ (adjusted percent)	35.4%	-	16.6%
<b>FPG (mg/dL)</b>			
Baseline (mean)	161.7	-	163.1
Change from baseline at Week 24 (adjusted mean <sup>‡</sup> )	-24.1	-	3.8
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-27.9 <sup>¶</sup> (-34.5, -21.4)	-	
<b>Body Weight (kg)</b>			
Baseline (mean)	91.02	-	89.23
Change from baseline (adjusted mean <sup>‡</sup> )	-2.14	-	-0.26
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-1.89 <sup>¶</sup> (-2.37, -1.40)	-	
<b>In Combination with Insulin with or without up to 2 Oral Antidiabetic Therapies</b>			
<b>Intent-to-Treat Population</b>	<b>N=194<sup>†</sup></b>	<b>N=211<sup>†</sup></b>	<b>N=193<sup>†</sup></b>
<b>HbA1c (%)</b>			
Baseline (mean)	8.6	8.6	8.5
Change from baseline (adjusted mean <sup>‡</sup> )	-0.9	-0.8	-0.3
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-0.6 <sup>¶</sup> (-0.7, -0.5)	-0.5 <sup>¶</sup> (-0.7, -0.4)	
<b>FPG (mg/dL)</b>			
Baseline (mean)	173.7	NT <sup>‡‡</sup>	170.0
Change from baseline (adjusted mean <sup>‡</sup> )	-21.7	NT <sup>‡‡</sup>	3.3
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-25.0 <sup>¶</sup> (-34.3, -15.8)	NT <sup>‡‡</sup>	
<b>Body Weight (kg)</b>			
Baseline (mean)	94.6	93.2	94.2
Change from baseline (adjusted mean <sup>‡</sup> )	-1.7	-1.0	0.0
Difference from placebo (adjusted mean <sup>‡</sup> ) (95% CI)	-1.7 <sup>¶</sup> (-2.2, -1.2)	-1.0 <sup>¶</sup> (-1.5, -0.5)	

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

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

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

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

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

<sup>#</sup> 2-hour PPG level as a response to a 75-gram oral glucose tolerance test (OGTT).

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

<sup>††</sup> p-value <0.05 versus placebo.

<sup>‡‡</sup> NT: Not formally tested because of failing to achieve a statistically significant difference in an endpoint that was earlier in the testing sequence.

### Combination Therapy with Exenatide-Extended Release as Add-On to Metformin

A total of 694 adult patients with type 2 diabetes and inadequate glycemic control (HbA1c  $\geq 8.0$ )

and  $\leq 12.0\%$ ) on metformin, were evaluated in a 28-week double-blind, active-controlled study to compare Forxiga in combination with exenatide extended-release (a GLP-1 receptor agonist) to Forxiga alone and exenatide extended-release alone, as add-on to metformin (NCT02229396). Patients on metformin at a dose of at least 1,500 mg per day were randomized following a 1-week placebo lead-in period to receive either Forxiga 10 mg once daily (QD) in combination with exenatide extended-release 2 mg once weekly (QW), Forxiga 10 mg QD, or exenatide extended-release 2 mg QW.

At week 28, Forxiga in combination with exenatide extended-release provided statistically significantly greater reductions in HbA1c (-1.77%) compared to Forxiga alone (-1.32%,  $p=0.001$ ) and exenatide extended-release alone (-1.42%,  $p=0.012$ ). Forxiga in combination with exenatide extended-release provided statistically significantly greater reductions in FPG (-57.35 mg/dL) compared to Forxiga alone (-44.72 mg/dL,  $p=0.006$ ) and exenatide extended-release alone (-40.53,  $p < 0.001$ ).

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

The efficacy of Forxiga was assessed in a study of diabetic patients with moderate renal impairment (252 patients with mean eGFR 45 mL/min/1.73 m<sup>2</sup>). Forxiga did not show efficacy in this study. The placebo-corrected mean HbA1c change at 24 weeks was -0.1% (95% CI [-0.4%, 0.2%]) for both Forxiga 5 mg (n=83) and 10 mg (n=82).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### How Supplied

Forxiga (dapagliflozin) tablets have markings on both sides and are available in the strengths and packages listed in Table 14.

**Table 14: Forxiga Tablet Presentations**

Tablet Strength	Film-Coated Tablet Color/Shape	Tablet Markings	Package Size
5 mg	yellow, biconvex, round	“5” engraved on one side and “1427” engraved on the other side	2*14 Alu-Alu blister pack in carton
10 mg	yellow, biconvex, diamond-shaped	“10” engraved on one side and “1428” engraved on the other side	2*14 Alu-Alu blister pack in carton

## Storage and Handling

Store below 30°C

## 17 PATIENT COUNSELING INFORMATION

### Instructions

Inform patients of the potential risks and benefits of Forxiga and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1c testing, recognition and management of hypoglycemia and hyperglycemia, and assessment of diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

Instruct patients to take Forxiga only as prescribed. If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of Forxiga at the same time.

Inform patients that the most common adverse reactions associated with use of Forxiga are genital mycotic infections, nasopharyngitis, and urinary tract infections.

Instruct patient to immediately inform her healthcare provider if she is pregnant or plans to become pregnant. Based on animal data, Forxiga may cause fetal harm in the second and third trimesters of pregnancy.

Instruct patient to immediately inform her healthcare provider if she is breastfeeding or planning to breastfeed. It is not known if Forxiga is excreted in breast milk; however, based on animal data, Forxiga may cause harm to nursing infants.

### Hypotension

Inform patients that symptomatic hypotension may occur with Forxiga and advise them to contact their healthcare provider if they experience such symptoms [see *Warnings and Precautions (5.1)*]. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

### Genital Mycotic Infections in Females (e.g., Vulvovaginitis)

Inform female patients that vaginal yeast infections may occur and provide them with

information on the signs and symptoms of vaginal yeast infections. Advise them of treatment options and when to seek medical advice [see *Warnings and Precautions (5.7)*].

### **Ketoacidosis**

Inform patients that ketoacidosis has been reported during use of dapagliflozin. If symptoms of ketoacidosis occur (including nausea, vomiting, abdominal pain, malaise and shortness of breath), instruct patients to check ketones (when possible) and seek medical advice immediately, even if blood glucose is not elevated [see *Warnings and Precautions (5.2)*].

### **Urinary Tract Infections**

Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice promptly if such symptoms occur [see *Warnings and Precautions (5.4)*].

### **Genital Mycotic Infections in Males (e.g., Balanitis)**

Inform male patients that yeast infections of the penis (e.g., balanitis or balanoposthitis) may occur, especially in patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice [see *Warnings and Precautions (5.4)*].

### **Hypersensitivity Reactions**

Inform patients that serious hypersensitivity reactions (e.g., urticaria and angioedema) have been reported with Forxiga. Advise patients to immediately report any signs or symptoms suggesting allergic reaction or angioedema, and to take no more of the drug until they have consulted prescribing physicians.

### **Bladder Cancer**

Inform patients to promptly report any signs of macroscopic hematuria or other symptoms potentially related to bladder cancer.

### **Pregnancy**

Advise pregnant patients of the potential risk to a fetus with treatment with Forxiga. Instruct patients to immediately inform their healthcare provider if pregnant or planning to become pregnant [see *Use in Specific Populations (8.1)*].

## Lactation

Advise patients that use of Forxiga is not recommended while breastfeeding [see *Use in Specific Populations* (8.2)].

## Laboratory Tests

Due to its mechanism of action, patients taking Forxiga will test positive for glucose in their urine.

Forxiga is a registered trademark of the AstraZeneca group of companies.

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