דצמבר 2021

רופא/ה נכבד/ה
רוקח/ת נכבד/ה שלום רב,

<u>פרסום עדכון לגבי התכשיר:</u>
<u>Forxiga 5 mg 152-57-34012-00/01</u>
<u>Forxiga 10 mg 152-58-34013-00/01</u>

חברת אסטרהזניקה ישראל מבקשת להודיע על רישום התוויה נוספת עבור פורסיגה להפחתת הסיכון לירידה מתמשכת ב eGFR, הגעה למחלת כליה סופנית, תמותה קרדיווסקולרית ואישפוזים על רקע אי ספיקת לב במבוגרים עם מחלת כליה כרונית בסיכון להתדרדרות.

הרכב:

Each tablet contains dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin.
Each tablet contains dapagliflozin propanediol monohydrate equivalent to 10 mg dapagliflozin.

התווית:

Forxiga is indicated
in adults aged 18 years and older for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance.
- in addition to other medicinal products for the treatment of type 2 diabetes.

to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction.

to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.

Limitations of Use

- FORXIGA is not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of immunosuppressive therapy for kidney disease. FORXIGA is not expected to be effective in these populations..

העלון לרופא והעלון לצרכן התעדכנו בעקבות תוספת ההתוויה, בהתאם להוראות משרד הבריאות בתאריך **דצמבר 2021.**

<u>העדכונים המהותיים בעלון לרופא הינם:</u>

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

~~Type 2 Diabetes Mellitus~~
Forxiga is indicated
in adults aged 18 years and older for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- <u>as monotherapy</u> when metformin is considered inappropriate due to intolerance.

- in addition to other medicinal products for the treatment of type 2 diabetes.

For study results with respect to combination of therapies, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.

Heart Failure

FORXIGA is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction.

Chronic kidney disease

FORXIGA is indicated to to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.

Limitations of Use:

- FORXIGA is not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of immunosuppressive therapy for kidney disease. FORXIGA is not expected to be effective in these populations.

4.2 Posology and method of administration

Posology

Type 2 Diabetes Mellitus

The recommended dose is 10 mg dapagliflozin orally once daily

When dapagliflozin is used to treat T2DM in combination with insulin or an insulin secretagogue, such as a sulphonylurea, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia (see sections 4.5 and 4.8).

Heart Failure

The recommended dose of FORXIGA is 10 mg orally once daily.

Special populations

Renal impairment

See Table 1 for dosage recommendations based on estimated glomerular filtration rate (eGFR).

Table 1. FORXIGA Dosing Recommendations for Patients Based on Renal FunctionRecommended Dosage

Treatment/ Patient Population eGFR (mL/min/1.73 m^2)	Recommended Dosage based on eGFR (mL/min/1.73 m^2, CKD-EPI)			
	greater than 45	30 to 45	less than 30	ESRD/Dialysis
Use for glycemic control in patients with T2DM **eGFR 45 or greater**	No dose adjustment For all indications, the recommended starting dose is 10 mg orally once daily.	Not recommended	Contraindicated	
To reduce risk of CV death and hHF in patients with HFrEF, with or without T2DM **eGFR 25 to less than 45**	No dose adjustment 10 mg orally once daily*.		Insufficient data	Contraindicated

eGFR less than 25	Initiation is not recommended, however patients may continue 10 mg orally once daily to reduce the risk of eGFR decline, ESKD, CV death and hHF.
On dialysis	Contraindicated.

eGFR: Estimated glomerular filtration rate, CKD-EPI: Chronic kidney disease epidemiology collaboration equation, T2DM: Type 2 diabetes mellitus, hHF: hospitalization for heart failure, HFrEF: Heart failure with reduced ejection fraction, , CV: Cardiovascular, ESRD: End Stage Renal Disease

* FORXIGA is not recommended for the treatment of insufficiently use to improve glycemic controlled in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m^2. FORXIGA is likely to be ineffective in this setting based upon its mechanism of action.

hHF: hospitalization for heart failure, CV: Cardiovascular, ESKD: End Stage Kidney Disease.

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Elderly (≥ 65 years)
In general, no dosage adjustment is recommended based on age. Renal function and risk of volume depletion should be taken into account (see sections 4.4 and 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
FORXIGA is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m2
Patients on dialysis

4.4 Special warnings and precautions for use
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Ketoacidosis *in Patients with Diabetes Mellitus*
Reports of ketoacidosis, including life-threatening and fatal cases, have been identified in post marketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including FORXIGA. In placebo-controlled trials of patients with type 1 diabetes mellitus, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo.
The reports were seen in patients treated with type 2 diabetes and type 1 diabetes. FORXIGA is not indicated for the treatment of patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.

Cardiac failure
There is no Eexperience in clinical studies with dapagliflozin in NYHA class IV is limited.

Chronic kidney disease
There is no experience with dapagliflozin for the treatment of chronic kidney disease in patients without diabetes who do not have albuminuria. Patients with albuminuria may benefit more from treatment with dapagliflozin.
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4.8 Undesirable effects
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Summary of the safety profile
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FORXIGA has been evaluated in clinical trials in patients with type 2 diabetes mellitus, and in patients with heart failure, and in patient with chronic kidney disease. The overall safety profile of FORXIGA was consistent across the studied indications. Severe hypoglycemia and diabetic ketoacidosis (DKA) were observed only in patients with diabetes mellitus.

The most frequently reported adverse reactions across the clinical studies were genital infections.

Heart failure
In the dapagliflozin cardiovascular outcome study in patients with heart failure with reduced ejection fraction (DAPA-HF study), 2,368 patients were treated with dapagliflozin 10 mg and 2,368 patients with placebo for a median exposure time of 18 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, and patients with eGFR ≥ 30 mL/min/1.73 m^2.
The overall safety profile of dapagliflozin in patients with heart failure was consistent with the known safety profile of dapagliflozin.

Chronic kidney disease
In the dapagliflozin renal outcome study in patients with chronic kidney disease (DAPA-CKD), 2,149 patients were treated with dapagliflozin 10 mg and 2,149 patients with placebo for a median exposure time of 27 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, with eGFR ≥ 25 to ≤ 75 mL/min/1.73 m2, and albuminuria (urine albumin creatinine ratio [UACR] ≥ 200 and ≤ 5000 mg/g). Treatment was continued if eGFR fell to levels below 25 mL/min/1.73 m2.
The overall safety profile of dapagliflozin in patients with chronic kidney disease was consistent with the known safety profile of dapagliflozin.

Tabulated list of adverse reactions
The following adverse reactions have been identified in the placebo-controlled clinical ~~trials~~studies and postmarketing surveillance. None were found to be dose-related. Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: very common (≥ 1/10), common (≥ 1/100 to< 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 2 Adverse reactions in placebo-controlled clinical studies[a] and postmarketing experience

System organ class	Very common	Common*	Uncommon**	Rare	Very rare
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin) [b]		Volume depletion [b,e] Thirst**	Diabetic ketoacidosis[i] (when used in type 2 diabetes mellitus) [b,i,k]	

Description of selected adverse reactions
Vulvovaginitis, balanitis and related genital infections
….
In the DAPA-HF study, no patient reported serious adverse events of genital infections in the dapagliflozin group and on in the placebo group. There were 7 (0.3%) patients with adverse events leading to discontinuation due to genital infections in the dapagliflozin group and none in the placebo group.

In the DAPA-CKD study, there were 3 (0.1%) patients with serious adverse events of genital infections in the dapagliflozin group and none in the placebo group. There were 3 (0.1%) patients with adverse events leading to discontinuation due to genital infections in the dapagliflozin group and none in the placebo group. Serious adverse events of genital infections or adverse events leading to discontinuation due to genital infections were not reported for any patients without diabetes.
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Hypoglycaemia
….

In the ~~dapagliflozin cardiovascular outcomes~~ DECLARE study, no increased risk of major hypoglycaemia was observed with dapagliflozin therapy compared with placebo. Major events of hypoglycaemia were reported in 58 (0.7%) patients treated with dapagliflozin and 83 (1.0%) patients treated with placebo.

In the DAPA-HF study, major events of hypoglycaemia were reported in 4 (0.2%) patients in both the dapagliflozin and placebo treatment groups and observed only in patients with 2 diabetes mellitus

In the DAPA-CKD study, major events of hypoglycaemia were reported in 14 (0.7%) patients in the dapagliflozin group and 28 (1.3%) patients in the placebo group and observed only in patients with type 2 diabetes mellitus

Volume depletion

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In the DAPA-HF study, the numbers of patients with events suggestive of volume depletion were 170 (7.2%) in the dapagliflozin group and 153 (6.5%) in the placebo group. There were fewer patients with serious events of symptoms suggestive of volume depletion in the dapagliflozin group (23 [1.0%]) compared with the placebo group (38 [1.6%]). Results were similar irrespective of presence of diabetes at baseline and baseline eGFR

In the DAPA-CKD study, the numbers of patients with events suggestive of volume depletion were 120 (5.6%) in the dapagliflozin group and 84 (3.9%) in the placebo group. There were 16 (0.7%) patients with serious events of symptoms suggestive of volume depletion in the dapagliflozin group and 15 (0.7%) patients in the placebo group.

Diabetic ketoacidosis in type 2 diabetes mellitus

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In the DAPA-HF study, events of DKA were reported in 3 paients with type 2 diabetes mellitus in the dapagliflozin group and none in the palcebo group

In the DAPA-CKD study, events of DKA were not reported in any patient in the dapagliflozin group and in 2 patients with type 2 diabetes mellitus in the placebo group.

Urinary tract infections

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In the DAPA-HF study, the numbers of patients with serious adverse events of urinary tract infections were 14 (0.6%) in the dapagliflozin group and 17 (0.7%) in the placebo group. There were 5 (0.2%) patients with adverse events leading to discontinuation due to urinary track infections in each of the dapagliflozin and placebo groups

In the DAPA-CKD study, the numbers of patients with serious adverse events of urinary tract infections were 29 (1.3%) in the dapagliflozin group and 18 (0.8%) in the placebo group. There were 8 (0.4%) patients with adverse events leading to discontinuations due to urinary tract infections in the dapagliflozin group and 3 (0.1%) in the placebo group. The numbers of patients without diabetes reporting serious adverse events of urinary tract infections or adverse events leading to discontinuation
due to urinary tract infections were similar between treatment groups (6 [0.9%] versus 4 [0.6%] for serious adverse events, and 1 [0.1%] versus 0 for adverse events leading to discontinuation, in the dapagliflozin and placebo groups, respectively).

Increased creatinine

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In the DAPA-HF study ,eGFR decreased over time in both the dapagliflozin group and the placebo group. The initial decrease in mean eGFR was -4.3 mL/min/1.73 m^2 in the dapagliflozin group and -1.1 mL/min/1.73 m^2 in the placebo group. At 20 months, change from baseline in eGFR was

similar between the treatment groups: -5.3 mL/min/1.73 m^2 for dapagliflozin and -4.5 mL/min/1.73 m^2 for placebo

~~**DAPA-HF Heart Failure Study**~~
~~No new adverse reactions were identified in the DAPA-HF heart failure study.~~

In the DAPA-CKD study, eGFR decreased over time in both the dapagliflozin group and the placebo group. The initial (day 14) decrease in mean eGFR was -4.0 mL/min/1.73 m2 in the dapagliflozin group and -0.8 mL/min/1.73 m2 in the placebo group. At 28 months, change from baseline in eGFR was -7.4 mL/min/1.73 m2 in the dapagliflozin group and -8.6 mL/min/1.73 m2 in the placebo group.

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5. Pharmacological properties

5.1 Pharmacodynamic properties

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Mechanism of action
Dapagliflozin is a highly potent (Ki: 0.55 nM), selective and reversible inhibitor of SGLT2.

~~The 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 hyperglycaemia in type 2 diabetes, reabsorption of filtered glucose continues.~~

Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which increases tubuloglomerular feedback and reduces intraglomerular pressure. This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodelling and preserve renal function. Other effects include an increase in haematocrit and reduction in body weight. The cardiac and renal benefits of dapagliflozin are not solely dependent on the blood glucoselowering effect and not limited to patients with diabetes as demonstrated in the DAPA-HF and DAPACKD studies

Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24-hour dosing interval and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. ~~.~~ Thus, in subjects with normal blood glucose, dapagliflozin has a low propensity to cause hypoglycaemia. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Improvement in homeostasis model assessment for beta cell function (HOMA beta-cell) has been observed in clinical studies with ~~Forxiga~~dapagliflozin.

~~Urinary glucose excretion (glucuresis) induced by dapagliflozin is associated with caloric loss and reduction in weight. Inhibition of glucose and sodium co-transport by dapagliflozin is also associated with mild diuresis and transient natriuresis.~~

The SGLT2 is selectively expressed in the kidney. Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is > 1,400 times more selective for SGLT2 versus SGLT1, the major transporter in the gut responsible for glucose absorption.
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Cardiovascular and renal outcomes

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At baseline, 10.0% of patients had a history of heart failure. Mean eGFR was 85.2 mL/min/1.73 m^2, 7.4% of patients had eGFR < 60 mL/min/1.73 m^2, and 30.3% of patients had micro- or macroalbuminuria (~~urine albumin to creatinine ratio~~ [UACR] ≥ 30 to ≤ 300 mg/g or > 300 mg/g, respectively).

Most patients (98. ~~1~~%) used one or more diabetic ~~medications~~ medicinal products at baseline, ~~82.0% of the patients were being treated with~~ including metformin, ~~40.9% with~~(82%), insulin, ~~42.7% with a~~ (41%) and sulfonylurea (43%), ~~16.8% with a DPP4 inhibitor and 4.4% with a GLP-1 agonist.~~

~~Approximately 81.3% of patients were treated with ACE-I or ARB, 75.0% with statins, 61.1% with antiplatelet therapy, 55.5% with acetylsalicylic acid, 52.6% with beta-blockers, 34.9% with calcium channel blockers, 22.0% with thiazide diuretics and 10.5% with loop diuretics.~~

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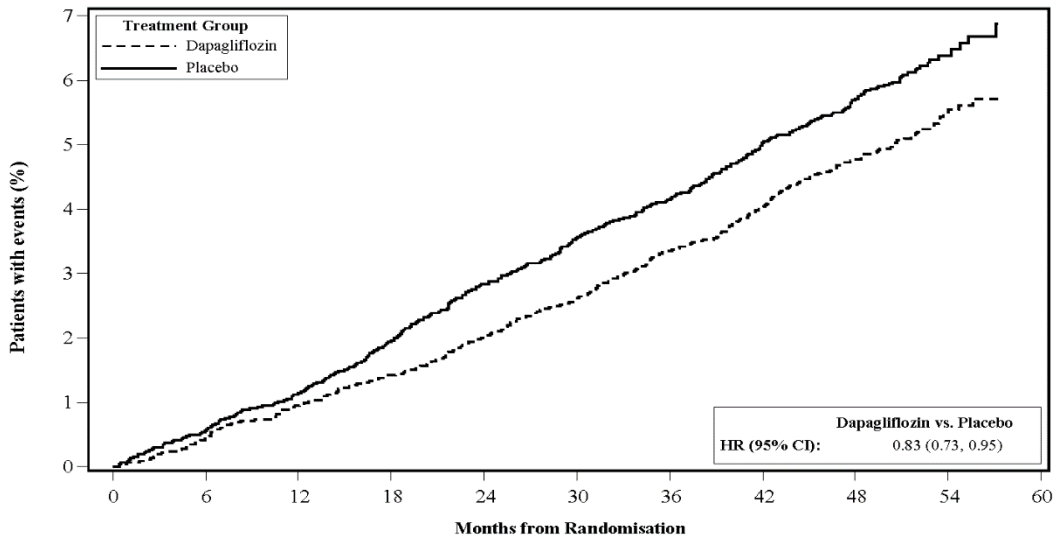
Heart failure or cardiovascular death

Dapagliflozin 10 mg ~~was superior to~~ demonstrated superiority versus placebo in preventing the ~~primary~~ composite ~~endpoint~~ of hospitalisation for heart failure or cardiovascular death (Figure 1). The difference in treatment effect was driven by hospitalisation for heart failure, with no difference in cardiovascular death (Figure 2).

The treatment benefit of dapagliflozin over placebo was observed both in patients with and without established cardiovascular disease, with and without heart failure at baseline, and was consistent across key subgroups, including age, gender, renal function (eGFR) and region.

Figure 1: Time to first occurrence of hospitalisation for heart failure or cardiovascular death



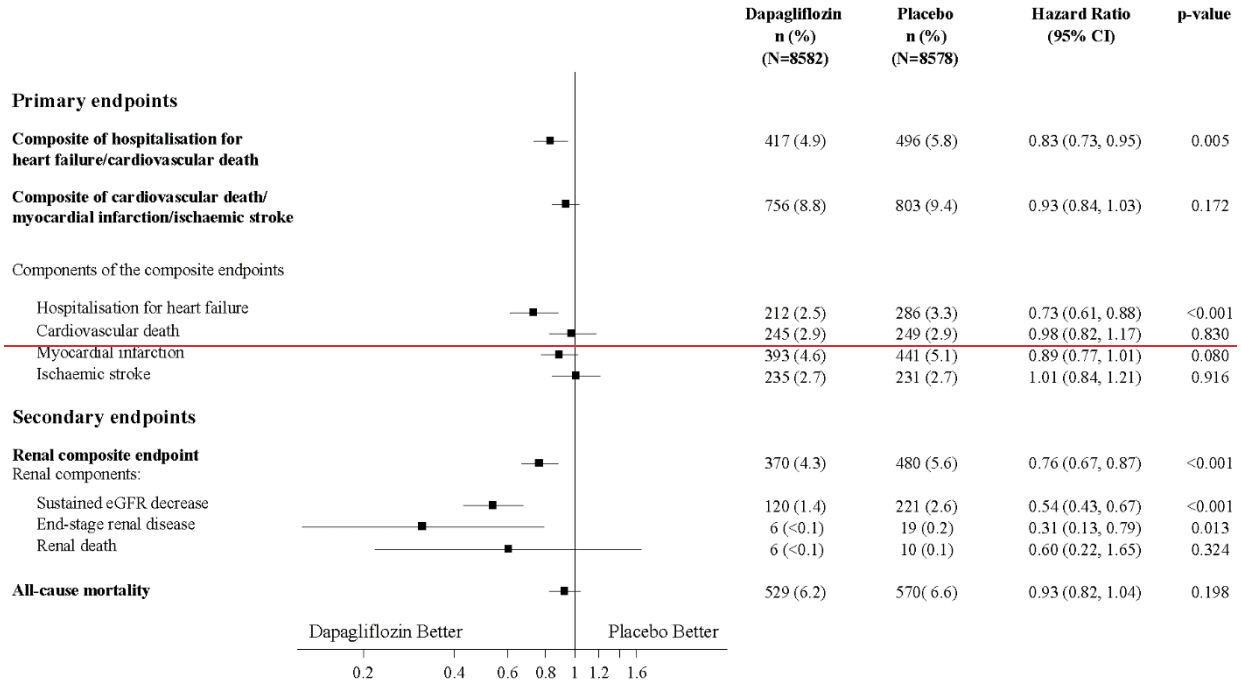
Patients at risk

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

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

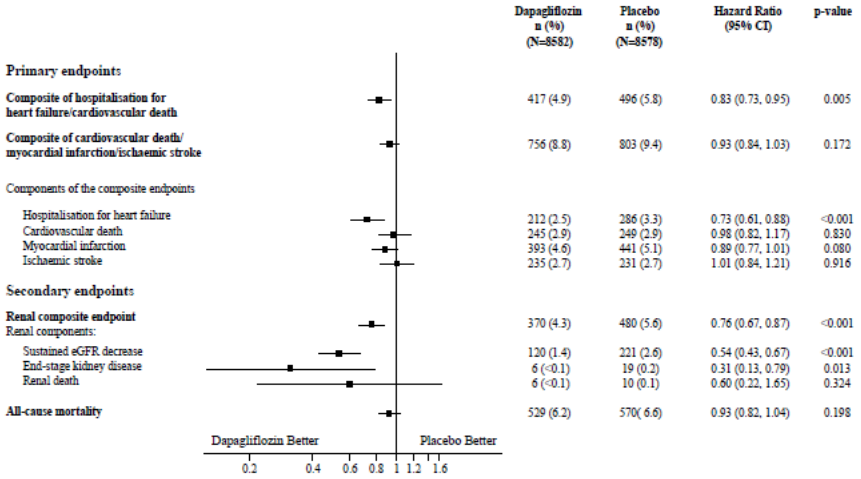
Results on primary and secondary endpoints are displayed in Figure 2. Superiority of dapagliflozin over placebo was not demonstrated for MACE (p=0.172). The renal composite endpoint and all-cause mortality were therefore not tested as part of the confirmatory testing procedure.

Figure 2: Treatment effects for the primary composite endpoints and their components, and the secondary endpoints and components



	Dapagliflozin n (%) (N=8582)	Placebo n (%) (N=8578)	Hazard Ratio (95% CI)	p-value
Primary endpoints				
Composite of hospitalisation for heart failure/cardiovascular death	417 (4.9)	496 (5.8)	0.83 (0.73, 0.95)	0.005
Composite of cardiovascular death/ myocardial infarction/ischaemic stroke	756 (8.8)	803 (9.4)	0.93 (0.84, 1.03)	0.172
Components of the composite endpoints				
Hospitalisation for heart failure	212 (2.5)	286 (3.3)	0.73 (0.61, 0.88)	<0.001
Cardiovascular death	245 (2.9)	249 (2.9)	0.98 (0.82, 1.17)	0.830
Myocardial infarction	393 (4.6)	441 (5.1)	0.89 (0.77, 1.01)	0.080
Ischaemic stroke	235 (2.7)	231 (2.7)	1.01 (0.84, 1.21)	0.916
Secondary endpoints				
Renal composite endpoint	370 (4.3)	480 (5.6)	0.76 (0.67, 0.87)	<0.001
Renal components:				
Sustained eGFR decrease	120 (1.4)	221 (2.6)	0.54 (0.43, 0.67)	<0.001
End-stage renal disease	6 (<0.1)	19 (0.2)	0.31 (0.13, 0.79)	0.013
Renal death	6 (<0.1)	10 (0.1)	0.60 (0.22, 1.65)	0.324
All-cause mortality	529 (6.2)	570(6.6)	0.93 (0.82, 1.04)	0.198

Figure 2: Treatment effects for the primary composite endpoints and their components, and the secondary endpoints and components



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All-cause mortality	529 (6.2)	570(6.6)	0.93 (0.82, 1.04)	0.198

Renal composite endpoint defined as: sustained confirmed ≥ 40% decrease in eGFR to eGFR <60 mL/min/1.73 m^2 and/or end-stage ~~renal~~ kidney disease (dialysis ≥ 90 days or kidney transplantation, sustained confirmed eGFR < 15 mL/min/1.73 m^2) and/or renal or cardiovascular death.

p-values are two-sided. ~~Since superiority of dapagliflozin over placebo was demonstrated for one of the dual primary endpoints only, and not for MACE, nominal~~ p-values ~~are shown~~ for the secondary ~~renal composite endpoint and all-cause mortality. Nominal p-values are also shown~~endpoints and for single components are nominal. Time to first event was analysed in a Cox proportional hazards model. The number of first events for the single components are the actual number of first events for each component and does not add up to the number of events in the composite endpoint.

CI=confidence interval.

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Chronic Kidney Disease

The Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease (DAPA-CKD, NCT03036150) was an international, multicenter, randomized, double-blind, placebo-controlled study in patients with chronic kidney disease (CKD) (eGFR between 25 and 75 mL/min/1.73 m2) and albuminuria (urine albumin creatinine ratio [UACR] between 200 and 5000 mg/g) who were receiving standard of care background therapy, including a maximally tolerated, labeled daily dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). The trial excluded patients with autosomal dominant or autosomal recessive polycystic kidney disease, lupus nephritis, or ANCA-associated vasculitis and patients requiring cytotoxic, immunosuppressive, or immunomodulatory therapies in the preceding 6 months.

The primary objective was to determine whether FORXIGA reduces the incidence of the composite endpoint of ≥50% sustained decline in eGFR, progression to end-stage kidney disease (ESKD) (defined as sustained eGFR<15 mL/min/1.73 m2, initiation of chronic dialysis treatment or renal transplant), CV or renal death.

A total of 4304 patients were randomized equally to FORXIGA 10 mg or placebo and were followed for a median of 28.5 months.

The mean age of the study population was 62 years and 67% were male. The population was 53% White, 4% Black or African-American, and 34% Asian; 25% were of Hispanic or Latino ethnicity.

At baseline, mean eGFR was 43 mL/min/1.73 m2, 44% of patients had an eGFR 30 mL/min/1.73m2 to less than 45 mL/min/1.73m2, and 15% of patients had an eGFR less than 30 mL/min/1.73m2. Median UACR was 950 mg/g. A total of 68% of the patients had type 2 diabetes mellitus at randomization. The most common etiologies of CKD were diabetic nephropathy (58%), ischemic/hypertensive nephropathy (16%), and IgA nephropathy (6%).

At baseline, 97% of patients were treated with ACEi or ARB. Approximately 44% were taking antiplatelet agents, and 65% were on a statin.

FORXIGA reduced the incidence of the primary composite endpoint of ≥50% sustained decline in eGFR, progression to ESKD, CV or renal death (HR 0.61 [95% CI 0.51,0.72]; p<0.0001). The FORXIGA and placebo event curves separate by Month 4 and continue to diverge over the study period. The treatment effect reflected a reduction in ≥50% sustained decline in eGFR, progression to ESKD, and CV death.

There were few renal deaths during the trial (Table 12, Figure 4).

FORXIGA also reduced the incidence of the composite endpoint of CV death or hospitalization for heart failure (HR 0.71 [95% CI 0.55, 0.92], p=0.0089) and all-cause mortality (HR 0.69 [95% CI 0.53, 0.88], p=0.0035).

Table 12: Treatment Effect for the Primary Composite Endpoint, its Components, and Secondary Composite Endpoints, in the DAPA-CKD Study

	Patients with events (event rate)			
Efficacy Variable (time to first occurrence)	**FORXIGA 10 mg N=2152**	**Placebo N=2152**	**Hazard ratio (95% CI)**	**p-value**
Composite of ≥50% sustained eGFR decline, ESKD, CV or renal death	197 (4.6)	312 (7.5)	0.61 (0.51, 0.72)	<0.0001
≥50% sustained eGFR decline	112 (2.6)	201 (4.8)	0.53 (0.42, 0.67)	
ESKD*	109 (2.5)	161 (3.8)	0.64 (0.50, 0.82)	
CV Death	65 (1.4)	80 (1.7)	0.81 (0.58, 1.12)	
Renal Death	2 (<0.1)	6 (0.3)		
≥50% sustained eGFR decline, ESKD or renal death	142 (3.3)	243 (5.8)	0.56 (0.45, 0.68)	<0.0001
CV death or Hospitalization for Heart Failure	100 (2.2)	138 (3.0)	0.71 (0.55, 0.92)	0.0089

Table 12: Treatment Effect for the Primary Composite Endpoint, its Components, and Secondary Composite Endpoints, in the DAPA-CKD Study

	Patients with events (event rate)			
Efficacy Variable (time to first occurrence)	**FORXIGA 10 mg N=2152**	**Placebo N=2152**	**Hazard ratio (95% CI)**	**p-value**
Hospitalization for Heart Failure	37 (0.8)	71 (1.6)	0.51 (0.34, 0.76)	
All-Cause Mortality	101 (2.2)	146 (3.1)	0.69 (0.53, 0.88)	0.0035

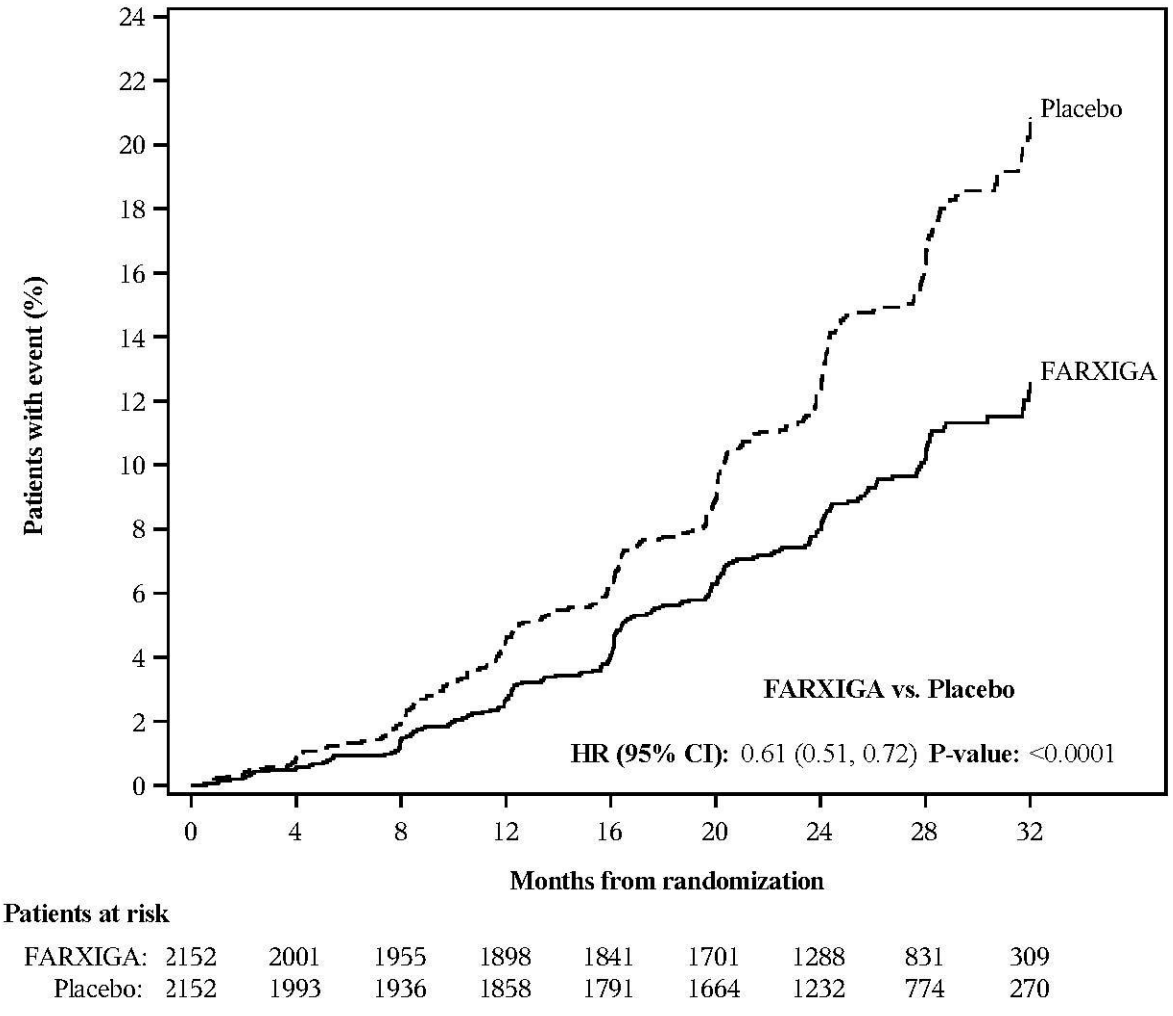
N=Number of patients, CI=Confidence interval, CV=Cardiovascular, ESKD=End stage kidney disease.

* ESKD is defined as sustained eGFR<15 mL/min/1.73 m^2, initiation of chronic dialysis treatment, or transplant.

NOTE: Time to first event was analyzed in a Cox proportional hazards model. Event rates are presented as the number of subjects with event per 100 patient years of follow-up.

There were too few events of renal death to compute a reliable hazard ratio.

Figure 4: Time to First Occurrence of the Primary Composite Endpoint, ≥50% Sustained Decline in eGFR, ESKD, CV or Renal Death (DAPA-CKD Study)



Patients at risk

FARXIGA:	2152	2001	1955	1898	1841	1701	1288	831	309
Placebo:	2152	1993	1936	1858	1791	1664	1232	774	270

Patients at risk is the number of subjects at risk at the beginning of the period. 1 month corresponds to 30 days. 2-sided p-value is displayed. HR, CI and p-value are from the Cox proportional hazard model.
HR=hazard ratio; CI=confidence interval; eGFR=estimated glomerular filtration rate; ESKD=end stage kidney disease; CV=cardiovascular; *vs*=versus.

The results of the primary composite endpoint were consistent across the subgroups examined, including CKD patients with and without type 2 diabetes mellitus, causes of CKD, age, biological sex, race, UACR, and eGFR.

DAPA-CKD enrolled a population with relatively advanced CKD at high risk of progression. Exploratory analyses of a randomized, double-blind, placebo-controlled trial conducted to determine the effect of FORXIGA on CV outcomes (the DECLARE trial) support the conclusion that FORXIGA is also likely to be effective in patients with less advanced CKD.

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5.2 Pharmacokinetic properties

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Special populations

Renal impairment

At steady-state (20 mg once-daily dapagliflozin for 7 days), subjects with type 2 diabetes mellitus and mild, moderate or severe renal impairment (as determined by iohexol plasma clearance) had mean systemic exposures of dapagliflozin were 45%, ~~of 32%, 60%~~100% and ~~87~~200% higher, respectively, than those of subjects with type 2 diabetes mellitus and normal renal function. There was no meaningful difference in exposure between patients with chronic kidney disease with and without type 2 diabetes.
Higher systemic exposure of dapagliflozin in patients with type 2 diabetes mellitus with renal impairment not result in a correspondingly higher 24-hour urinary glucose excretion.

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 subjects with type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. The impact of hemodialysis on dapagliflozin exposure is not known.

~~In the DAPA-HF study *[see Clinical Studies (14.3)]* that included patients with eGFR equal to or above 30 mL/min/1.73 m^2, there were 1926 (41%) patients with eGFR below 60 mL/min/1.73 m^2 and 719 (15%) with eGFR below 45 mL/min/1.73 m^2. No overall differences in safety or efficacy were seen in these patients compared to patients with normal renal function. No dose adjustment is recommended for HFrEF patients with eGFR 30 mL/min/1.73 m^2 and above *[see Dosage and Administration (2.4)]*~~

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Elderly (≥ 65 years)

There is no clinically meaningful increase in exposure based on age alone in subjects up to 70 years old. However, an increased exposure due to age-related decrease in renal function can be expected. There are insufficient data to draw conclusions regarding exposure in patients > 70 years old.

~~In the DAPA-HF study, 2714 (57%) out of 4744 patients with HFrEF were older than 65 years. Safety and efficacy were similar for patients age 65 years and younger and those older than 65.~~

העדכונים המהותיים בעלון לצרכן הינם:

1. למה מיועדת התרופה?

פורסיגה ניתנת לטיפול בסוכרת מסוג 2 במבוגרים (גיל 18 ומעלה), כאשר הסוכרת אינה מאוזנת בטיפול בתרופות אחרות לסוכרת, דיאטה ופעילות גופנית.
הרופא יכול להנחות אותך ליטול פורסיגה לבד, במקרה של אי סבילות למטפורמין, או בשילוב יחד עם תרופות אחרות לטיפול בסוכרת, כולל אינסולין.
בעת הטיפול בפורסיגה, חשוב לשלב דיאטה ופעילות גופנית, בהתאם להנחיות הרופא/הצוות הרפואי.

פורסיגה ניתנת כטיפול להורדת הסיכון למוות קרדיווסקולרי ולאשפוז כתוצאה מאי ספיקת לב במבוגרים עם אי ספיקת לב (NYHA class II-IV) עם מקטע פליטה ירוד.

פורסיגה ניתנת להפחתת הסיכון לירידה מתמשכת ב eGFR, הגעה למחלת כליה סופנית, תמותה קרדיוסקולרית ואישפוזים על רקע אי ספיקת לב במבוגרים עם מחלת כליה כרונית בסיכון להתדרדות

הגבלות שימוש
פורסיגה אינה מומלצת לטיפול במחלת כליות כרונית במטופלים עם מחלת כליות פוליציסטית או מטופלים הנדרשים או נזקקו לאחרונה לטפול לדיכוי מערכת החיסון למחלת הכליות. פורסיגה אינה צפויה להיות יעילה באוכלוסיות אלה
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2. לפני השימוש בתרופה

אין להשתמש בפורסיגה אם:

- יש לך רגישות יתר למרכיב הפעיל דפהגליפלוזין או לאחד ממרכיבי התרופה (ראה סעיף 6 "מידע נוסף" מטה).
- ~~יש לך בעיות כליה חמורות והנך נוטל פורסיגה להורדת הסוכר בדם.~~
- הנך מטופל בדיאליזה.

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אזהרות מיוחדות הנוגעות לשימוש בפורסיגה
לפני הטיפול בפורסיגה ספר לרופא, לרוקח או לאחות אם:

- הנך סובל מסוכרת ומבעיה כלייתית - ייתכן והרופא יורה לך לקחת תרופה אחרת או נוספת לטיפול ברמת הסוכר בדם.
- הנך סובל מבעיה בתפקודי הכבד- ייתכן והרופא יורה לך להתחיל במינון נמוך יותר.

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סוכרת וטיפול בכפות הרגליים
אם הנך סובל מסוכרת, חשוב לבדוק את כפות הרגליים באופן קבוע ולהתמיד בהמלצות הרפואיות הנוספות שניתנות בנושא טיפול בכפות הרגליים

~~**תפקוד כליות**~~
~~יש לבצע בדיקות תפקודי כליה לפני תחילת טיפול בפורסיגה ובמשך הטיפול.~~

אינטראקציות/תגובות בין תרופתיות:
אם אתה לוקח, או אם לקחת לאחרונה, תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח. במיוחד יש ליידע את הרופא או הרוקח אם אתה לוקח:

- תרופה משתנת (דיורטית), להוצאת נוזלים מהגוף~~, ייתכן והרופא ינחה אותך להפסיק ליטול פורסיגה. סימנים אפשריים לאיבוד של נוזלים רבים מהגוף מפורטים בתחילת סעיף 4 "תופעות לוואי".~~

3. כיצד תשתמש בתרופה?

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הרופא יכול לרשום פורסיגה עם תרופות אחרות ~~להורדת רמת הסוכר בדם. זו יכולה להיות תרופה הניתנת דרך הפה~~ ~~או בהזרקה כמו אינסולין או משפעלי הקולטן לחלבון~~ GLP-1. יש לזכור לקחת את התרופה האחרת שהרופא רשם. זה יעזור לך לקבל את התוצאות הטובות ביותר לבריאותך.

תזונה ופעילות גופנית

~~על מנת לאזן את הסוכרת, עליך להמשיך עדיין לשמור על דיאטה ופעילות גופנית, אף שאתה נוטל את התרופה.~~
~~חשוב להמשיך לפעול לפי הנחיות הרופא לגבי תזונה ופעילות גופנית בעת נטילת פורסיגה. אם הנך נמצא בתוכנית~~
~~דיאטה לאיזון המשקל בסוכרת, חשוב במיוחד להמשיך להתמיד בה, בעת נטילת פורסיגה.~~
דיאטה ופעילות גופנית יכולים לעזור לגוף שלך לאזן את רמת הסוכר בדם. אם יש לך סוכרת, חשוב להתמיד בכל תוכנית דיאטה ופעילות גופנית המומלצת על ידי הרופא שלך בעת נטילת פורסיגה

4. **<u>תופעות לוואי</u>**

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הפסק טיפול בפורסיגה ופנה בהקדם האפשרי לרופא, במידה ואתה מבחין באחת מתופעות הלוואי החמורות שלהלן:

- ~~**איבוד יתר של נוזלים מהגוף (התייבשות)**, תופעה לא שכיחה (עלולה להשפיע על עד 1 מתוך 100 מטופלים),~~
  ~~סימנים של התייבשות:~~
  - ~~יובש רב בפה או דביקות בפה, הרגשת צמא רב~~
  - ~~ישנוניות רבה או עייפות~~
  - ~~מיעוט או אי מתן שתן~~
  - ~~דופק מהיר~~

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תופעות לוואי אחרות בעת שימוש בפורסיגה:

תופעות לוואי שמופיעות לעיתים קרובות (משפיעות על עד 1 מתוך 10 מטופלים):

- מתן שתן רב יותר מהרגיל או ~~מתן~~ <u>צורך לתת</u> שתן לעיתים קרובות יותר
- שינוי ברמת הכולסטרול או השומנים בדם (נראה בבדיקות)
- ~~שינוי~~ <u>עלייה</u> בכמות תאי הדם האדומים בדם (נראה בבדיקות)
- ~~שינוי~~ <u>ירידה</u> ברמות ~~ה~~פינוי הקראטנין הכלייתי (נראה בבדיקות) בתחילת הטיפול

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תופעות לוואי לא שכיחות (משפיעות על עד 1 מתוך 100 מטופלים):

- <u>איבוד יתר של נוזלים מהגוף (התייבשות, סימנים יכולים לכלול: יובש רב בפה או דביקות בפה, מתן שתן מועט או אי מתן שתן, דופק מהיר)</u>

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מקרא לעדכונים המסומנים:
תוספת טקסט מהותי מסומנת בצבע אדום.
מחיקת טקסט מסומנת בקו חוצה בצבע כחול.

העלון מפורסם במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלו מודפס על ידי פניה לבעל הרישום.

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