ספטמבר 2020

רופא/ה נכבד/ה
רוקח/ת נכבד/ה שלום רב,

Forxiga 5 mg film-coated tablets : פרסום עדכון בעלוני התכשיר
Forxiga 10 mg film-coated tablets

הרכב:

Forxiga 5 mg film-coated tablets :
Each tablet contains dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin.

Forxiga 10 mg film-coated tablets:
Each tablet contains dapagliflozin propanediol monohydrate equivalent to 10 mg dapagliflozin.

התוויה:

Forxiga is indicated in adults aged 18 years and older for the treatment of insufficiency 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.

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.

חברת אסטרהזניקה ישראל מבקשת להודיע על עדכון עלון בהתאם להוראות משרד הבריאות בתאריך **ספטמבר 2020**

העדכון המהותי בעלון לרופא הוא:

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

- as monotherapy 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.

4.2 Posology and method of administration

Prior to initiation of Forxiga

Assess renal function prior to initiation of FORXIGA therapy and then as clinically indicated [see Warnings and Precautions].
In patients with volume depletion, correct this condition prior to initiation of FORXIGA [see Warnings and Precautions].

Posology
Type 2 Diabetes Mellitus
The recommended dose is 10 mg dapagliflozin orally once daily

When dapagliflozin is used 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

~~No dose adjustment is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m^2.~~
~~Use of FORXIGA is not recommended when the eGFR is less than 45 mL/min/1.73 m^2.~~
~~FORXIGA is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2 *[see Contraindications (4.3)].*~~

Table 1. FORXIGA Dosing Recommendations for Patients Based on Renal Function

Treatment/ Patient Population	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	No dose adjustment	Not recommended	Contraindicated	
To reduce risk of CV death and hHF in patients with HFrEF, with or without T2DM	No dose adjustment		Insufficient data	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

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

4.8 Undesirable effects

FORXIGA has been evaluated in clinical trials in patients with type 2 diabetes mellitus and in patients with heart failure. 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.

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DAPA-HF Heart Failure Study

No new adverse reactions were identified in the DAPA-HF heart failure study.

5.1 Pharmacodynamic properties

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Heart Failure with Reduced Ejection Fraction

Dapagliflozin And Prevention of Adverse outcomes in Heart Failure (DAPA-HF, NCT03036124) was an international, multicenter, randomized, double-blind, placebo-controlled study in patients with heart failure (New York Heart Association [NYHA] functional class II-IV) with reduced ejection fraction (left ventricular ejection fraction [LVEF] 40% or less) to determine whether FORXIGA reduces the risk of cardiovascular death and worsening heart failure.

Of 4744 patients, 2373 were randomized to FORXIGA 10 mg and 2371 to placebo and were followed for a median of 18 months. The mean age of the study population was 66 years, 77% were male and 70% were White, 5% Black or African-American, and 24% Asian.

At baseline, 68% patients were classified as NYHA class II, 32% class III, and 1% class IV; median LVEF was 32%. History of type 2 diabetes mellitus was present in 42%, and an additional 3% had type 2 diabetes mellitus based on a HbA1c ≥6.5% at both enrollment and randomization At baseline, 94% of patients were treated with ACEi, ARB or angiotensin receptor-neprilysin inhibitor (ARNI, including sacubitril/valsartan 11%), 96% with beta-blocker, 71% with mineralocorticoid receptor antagonist (MRA), 93% with diuretic, and 26% had an implantable device.

FORXIGA reduced the incidence of the primary composite endpoint of CV death, hospitalization for heart failure or urgent heart failure visit (HR 0.74 [95% CI 0.65, 0.85]; p<0.0001). All three components of the primary composite endpoint individually contributed to the treatment effect. The FORXIGA and placebo event curves separated early and continued to diverge over the study period (Table 11, Figures 6A, 6B and 6C).

Table 11: Treatment Effect for the Primary Composite Endpoint*, its Components* and All-Cause Mortality in the DAPA-HF Study

	Patients with events (event rate)			
Efficacy Variable (time to first occurrence)	**FORXIGA 10 mg N=2373**	**Placebo N=2371**	**Hazard ratio (95% CI)**	**p-value†**
Composite of Hospitalization for Heart Failure, CV Death or Urgent Heart Failure Visit	386 (11.6)	502 (15.6)	0.74 (0.65, 0.85)	<0.0001
Composite of CV Death or Hospitalization for Heart Failure	382 (11.4)	495 (15.3)	0.75 (0.65, 0.85)	<0.0001
Components of the composite endpoints‡				
CV Death	227 (6.5)	273 (7.9)	0.82 (0.69, 0.98)	
Hospitalization for Heart Failure or Urgent Heart Failure Visit	237 (7.1)	326 (10.1)	0.70 (0.59, 0.83)	
Hospitalization for Heart Failure	231 (6.9)	318 (9.8)	0.70 (0.59, 0.83)	
Urgent Heart Failure Visit	10 (0.3)	23 (0.7)	0.43 (0.20, 0.90)	

Table 11: Treatment Effect for the Primary Composite Endpoint*, its Components* and All-Cause Mortality in the DAPA-HF Study

	Patients with events (event rate)			
Efficacy Variable (time to first occurrence)	**FORXIGA 10 mg N=2373**	**Placebo N=2371**	**Hazard ratio (95% CI)**	**p-value†**
All-Cause Mortality‡	276 (7.9)	329 (9.5)	0.83 (0.71, 0.97)	

N=Number of patients, CI=Confidence interval, CV=Cardiovascular.

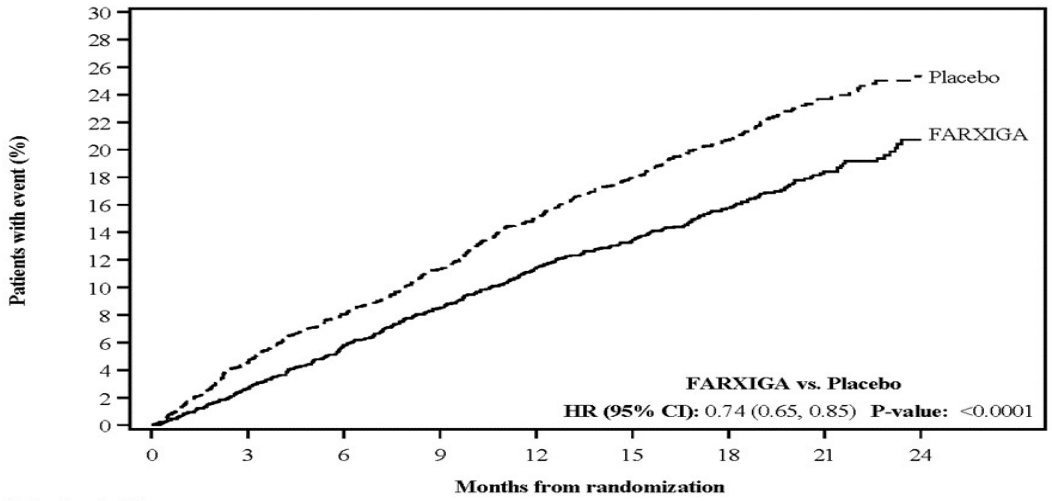
* Full analysis set.

† Two-sided p-values.

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

Figure 6: Kaplan-Meier Curves for the Primary Composite Endpoint (A), Cardiovascular Death (B), and Heart Failure Hospitalization (C)

Figure 6A: Time to the First Occurrence of the Composite of Cardiovascular Death, Hospitalization for Heart Failure or Urgent Heart Failure Visit

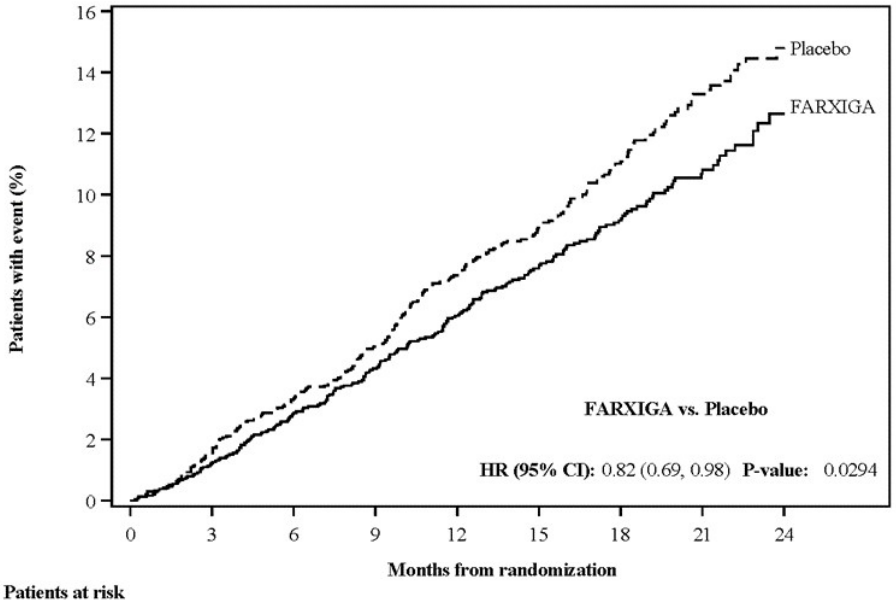


Patients at risk

FARXIGA:	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo:	2371	2258	2163	2075	1917	1478	1096	593	210

NOTE: An urgent heart failure visit was defined as an urgent, unplanned, assessment by a physician, e.g. in an Emergency Department, and requiring treatment for worsening heart failure (other than just an increase in oral diuretics).
Patients at risk is the number of patients at risk at the beginning of the period.
HR=Hazard ratio, CI=Confidence interval.

Figure 6B: Time to the First Occurrence of Cardiovascular Death

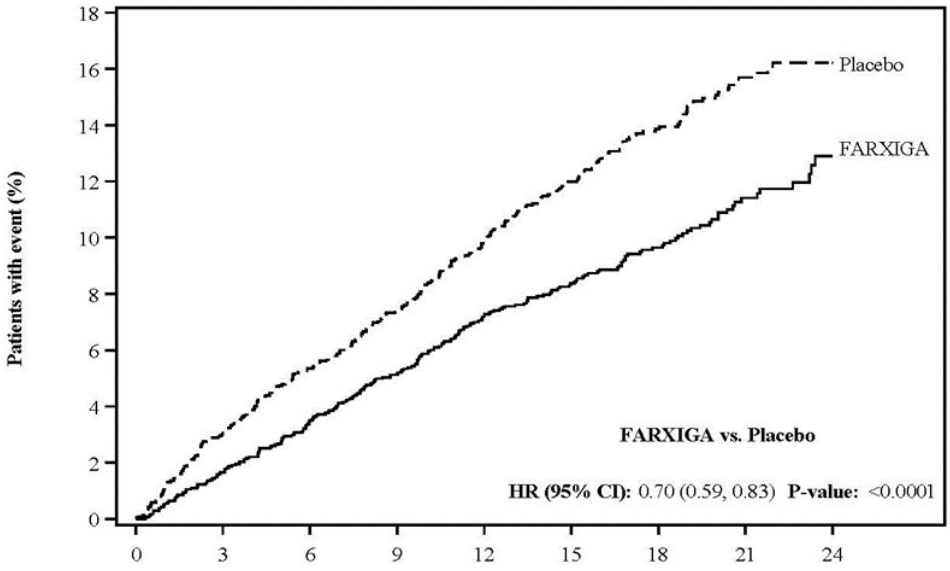


Patients at risk

FARXIGA:	2373	2339	2293	2248	2127	1664	1242	671	232
Placebo:	2371	2330	2279	2230	2091	1636	1219	664	234

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

Figure 6C: Time to the First Occurrence of Heart Failure Hospitalization



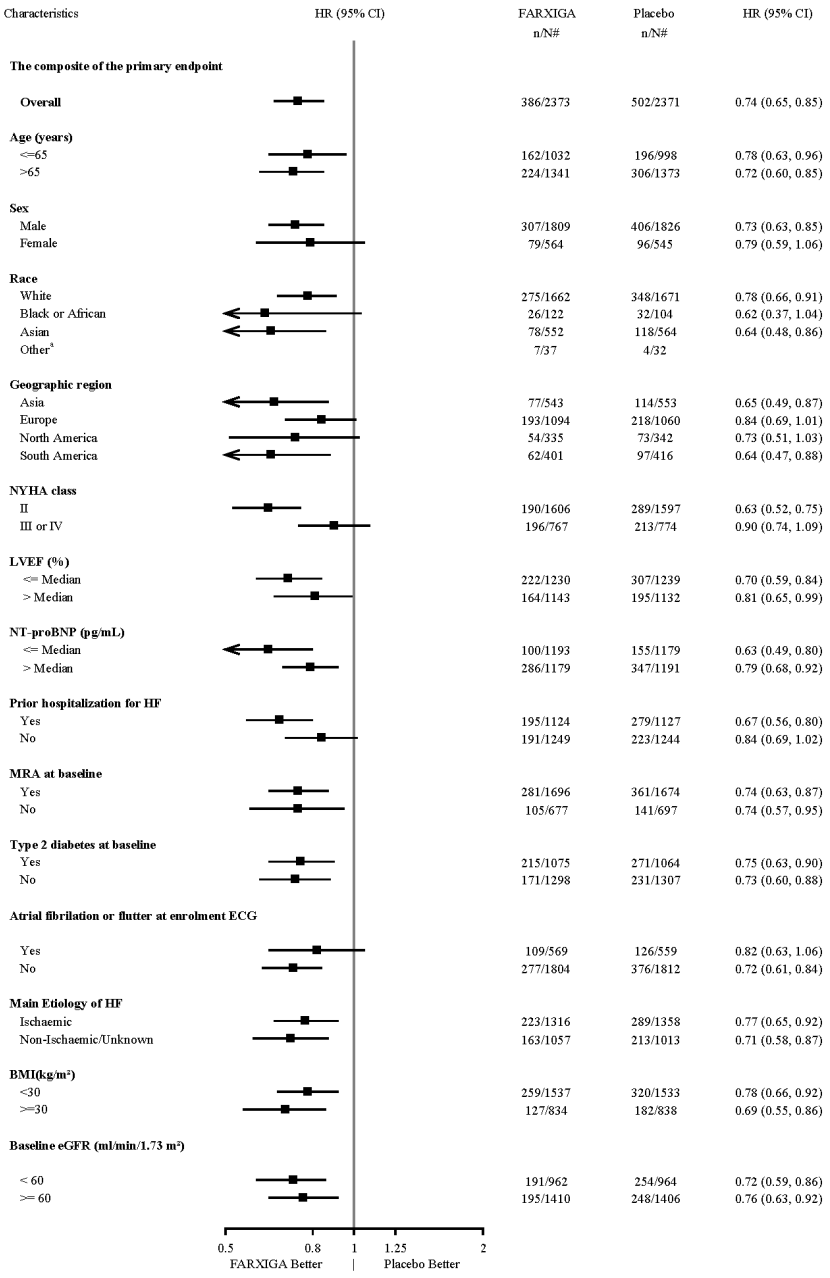
Patients at risk

FARXIGA:	2373	2306	2223	2153	2007	1563	1147	613	210
Placebo:	2371	2264	2168	2082	1924	1483	1101	596	212

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

FORXIGA reduced the total number of hospitalizations for heart failure (first and recurrent) events and CV death, with 567 and 742 total events in the FORXIGA-treated vs placebo group (Rate Ratio 0.75 [95% CI 0.65, 0.88]; p=0.0002).
The results of the primary composite endpoint were consistent across the subgroups examined, including heart failure patients with and without type 2 diabetes mellitus (Figure 7).

Figure 7: Treatment Effects for Primary Composite Endpoint (Cardiovascular Death and Heart Failure Events) Subgroup Analysis (DAPA-HF Study)



[a] Hazard ratio estimates are not presented for subgroups with less than 15 events in total, both arms combined.

n/N# Number of subjects with event/number of subjects in the subgroup.

NT-proBNP = N-terminal pro b-type natriuretic peptide, HF = Heart failure, MRA = mineralocorticoid receptor antagonist, ECG = electrocardiogram, eGFR = estimated glomerular filtration rate.

Note: The figure above presents effects in various subgroups, all of which are baseline characteristics. The 95% confidence limits that are shown do not take into account the number of comparisons made and may not reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

5.2 Pharmacokinetic properties

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 of 32%, 60% and 87% higher, respectively, than those of subjects with type 2 diabetes mellitus and normal renal function. 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)]*.

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.

העדכון המהותי בעלון לצרכן הוא:

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

2. לפני שימוש 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

מקרא לעדכונים המסומנים

הוספת טקסט מהותי מסומנת בצבע. מחיקת טקסט מסומנת בקו חוצה

העלונים מפורסמים במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום.

בכבוד רב,
קארין קנבל דובסון

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