דצמבר 2021

Jardiance 25 mg	Jardiance 10 mg
ג'ארדיאנס 25 מ"ג	ג'ארדיאנס 10 מ"ג
empagliflozin 25 mg	empagliflozin 10 mg
film-coated tablets	film-coated tablets

הנדון: עדכון עלונים

רופא/ה יקר/ה, רוקח/ת יקר/ה,

חברת בורינגר אינגלהיים ישראל בע"מ מבקשת להודיעכם על עדכון בעלון לרופא ובעלון לצרכן בהתאם להוראות משרד הבריאות.

התוויה:

JARDIANCE 10mg and 25mg are indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.

Jardiance 10mg is indicated:
to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure and reduced ejection fraction.

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השינויים המשמעותיים ביותר בעלונים סומנו מטה.

הסבר:
טקסט עם קו תחתי מציין טקסט שהוסף לעלון.
טקסט עם קו חוצה מציין טקסט שהוסר מן העלון.

למידע נוסף יש לעיין בעלון לרופא ובעלון לצרכן המאושרים.

העלונים המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות.
כמו כן, ניתן לקבלם על-ידי פנייה לבעל הרישום:
בורינגר אינגלהיים ישראל בע"מ, רח' מדינת היהודים 89 הרצליה פיתוח, ובטלפון 09-9730500.

ב ב ר כ ה,

מירי חזן
רוקחת ממונה
בורינגר אינגלהיים ישראל

עדכונים מהותיים בעלון לרופא

בסעיף 4. Indication and usage עודכן המידע הבא:

4 INDICATIONS AND USAGE

JARDIANCE 10mg and 25mg is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease.
- **Jardiance 10mg is indicated** :

to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure and reduced ejection fraction.

Limitations of Use

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

JARDIANCE is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73 m^2. JARDIANCE is likely to be ineffective in this setting based upon its mechanism of action.

בסעיף **5. DOSAGE AND ADMINISTRATION** עודכן המידע הבא:

5.2 Recommended Dosage

- The recommended dose of JARDIANCE is 10 mg once daily in the morning, taken with or without food.
- For additional glycemic control, the dose may be increased to 25 mg in patients tolerating JARDIANCE.
- Use for glycemic control is not recommended in patients with an eGFR less than 30 mL/min/1.73 m^2
- Data are insufficient to provide a dosing recommendation in patients;
  - who have type 2 diabetes and established cardiovascular disease with an eGFR less than 30 mL/min/1.73 m^2, or
  - who have heart failure with reduced ejection fraction with an eGFR less than 30 mL/min/1.73 m^2
  - JARDIANCE is contraindicated in patients on dialysis

~~*Monotherapy and add-on combination*~~

~~The recommended starting dose is 10 mg empagliflozin once daily in the morning, taken with or without food for monotherapy and add-on combination therapy with other glucose-lowering medicinal products including insulin. In patients tolerating empagliflozin 10 mg once daily, the dose can be increased to 25 mg once daily for additional glycemic control . The maximum daily dose is 25 mg~~

~~When empagliflozin is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia.~~

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~~**5.3 Patients with Renal Impairment**~~
~~JARDIANCE should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m^2.~~

~~No dose adjustment is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m^2.~~

~~JARDIANCE should be discontinued if eGFR is persistently less than 45 mL/min/1.73 m^2 *[see Warnings and Precautions (8.1, 8.3) and Use in Specific Populations (11.6)].*~~

בסעיף **7. CONTRAINDICATIONS** עודכן המידע הבא:

CONTRAINDICATIONS

- Hypersensitivity to empagliflozin or any of the excipients [see section 13] in JARDIANCE, reactions such as angioedema have occurred [see Warnings and Precautions (8.7)].
- ~~Severe renal impairment, end-stage renal disease, or~~ Patients on dialysis *[see Use in Specific Populations (11.6)]*.

בסעיף **9 ADVERSE REACTIONS** עודכן המידע הבא:

9.1 Clinical Trials Experience
[…]

~~Pool of Placebo-Controlled Trials evaluating JARDIANCE 10 and 25 mg~~

JARDIANCE has been evaluated in clinical trials in patients with type 2 diabetes mellitus and in patients with heart failure. The overall safety profile of JARDIANCE was generally consistent across the studied indications.

Clinical Trials in Patients with Type 2 Diabetes Mellitus

The data in Table 1 are derived from a pool of four 24-week placebo-controlled trials and 18-week data from a placebo-controlled trial with insulin in patients with type 2 diabetes. JARDIANCE was used as monotherapy in one trial and as add-on therapy in four trials *[see Clinical Studies (16)]*.

[…]

Clinical Trial in Patients with Heart Failure
The EMPEROR-Reduced study included 3726 patients with heart failure and reduced ejection fraction, treated with JARDIANCE 10 mg or placebo. No new adverse reactions were identified in the EMPEROR-Reduced heart failure study.
[…]

בסעיף **11 USE IN SPECIFIC POPULATIONS**. עודכן המידע הבא:

11.5 Geriatric Use

In ~~studies assessing the efficacy of empagliflozin in improving~~ glycemic control studies in patients with type 2 diabetes mellitus, a total of 2721 (32%) patients treated with JARDIANCE ~~empagliflozin~~ were 65 years of age and older, and 491 (6%) were 75 years of age and older. JARDIANCE is expected to have diminished glycemic efficacy in elderly patients with renal impairment *[see Use in Specific Populations (11.6)]*. The risk of volume depletion-related adverse reactions increased in patients who were 75 years of age and older to 2.1%, 2.3%, and 4.4% for placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg. The

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risk of urinary tract infections increased in patients who were 75 years of age and older to 10.5%, 15.7%, and 15.1% in patients randomized to placebo, JARDIANCE 10 mg, and JARDIANCE 25 mg, respectively *[see Warnings and Precautions (8.2) and Adverse Reactions (9.1)]*.

In the EMPEROR-Reduced study, a total of 1188 (64%) patients with heart failure 65 years of age and older were treated with 10 mg of JARDIANCE. Safety and efficacy were similar for patients 65 years and younger and those older than 65 years.

11.6 Renal Impairment

The efficacy and safety of JARDIANCE for glycemic control were evaluated in a study of patients with type 2 diabetes mellitus with mild and moderate renal impairment (eGFR 30 to less than 90 mL/min/1.73 m^2) *[see Clinical Studies (16)]*. In this study, 195 patients exposed to JARDIANCE had an eGFR between 60 and 90 mL/min/1.73 m^2, 91 patients exposed to JARDIANCE had an eGFR between 45 and 60 mL/min/1.73 m^2, and 97 patients exposed to JARDIANCE had an eGFR between 30 and 45 mL/min/1.73 m^2. The glucose lowering benefit of JARDIANCE 25 mg decreased in patients with worsening renal function. The risks of renal impairment, volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function *[see Warnings and Precautions (8.2)]*. Use of JARDIANCE for glycemic control in patients without established cardiovascular disease or cardiovascular risk factors is not recommended when eGFR is less than 30 mL/min/1.73 m^2.

In a large cardiovascular outcomes study of patients with type 2 diabetes and established cardiovascular disease, there were 1819 patients with eGFR below 60 mL/min/1.73 m^2. The cardiovascular death findings in this subgroup were consistent with the overall findings *[see Clinical Studies (16)]*.

In the study in patients with heart failure with reduced ejection fraction *[see Clinical Studies (16)]* patients with eGFR equal to or above 20 mL/min/1.73 m^2 were included. No dose adjustment is recommended for these patients. There is insufficient data to support a dosing recommendation in patients with eGFR below 30 mL/min/1.73 m^2.

Efficacy and safety studies with JARDIANCE did not enroll patients with an eGFR less than 20 mL/min/1.73 m^2. JARDIANCE is contraindicated in patients on dialysis *[see Contraindications (7)]*.

~~The efficacy and safety of JARDIANCE have not been established in patients with severe renal impairment, with ESRD, or receiving dialysis. JARDIANCE is not expected to be effective in these patient populations *[see Dosage and Administration (5.3), Contraindications (7) and Warnings and Precautions (8)]*.~~
[…]

בסעיף **CLINICAL PHARMACOLOGY** 14. עודכן המידע הבא:

14.1 Mechanism of Action
~~Sodium~~ Empagliflozin is an inhibitor of the sodium glucose co-transporter 2 (SGLT2) ~~is~~ the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. ~~Empagliflozin is an inhibitor of SGLT2~~. By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.
Empagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions such as lowering both pre-and afterload of the heart and downregulating sympathetic activity.

14.3 Pharmacokinetics

[…]

Specific Populations

Renal Impairment

In patients with type 2 diabetes mellitus with mild (eGFR: 60 to less than 90 mL/min/1.73 m^2), moderate (eGFR: 30 to less than 60 mL/min/1.73 m^2), and severe (eGFR: less than 30 mL/min/1.73 m^2) renal impairment and patients on dialysis due to ~~with~~ kidney failure/~~end stage renal disease (ESRD)~~, AUC of empagliflozin increased by approximately 18%, 20%, 66%, and 48%, respectively, compared to subjects with normal renal function. Peak plasma levels of empagliflozin were similar in patients with moderate renal impairment and patients on dialysis due to kidney failure~~/ESRD~~ compared to subjects with normal renal function. Peak plasma levels of empagliflozin were roughly 20% higher in patients with mild and severe renal impairment as compared to subjects with normal renal function. Population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased, with a decrease in eGFR leading to an increase in drug exposure. However, the fraction of empagliflozin that was excreted unchanged in urine, and urinary glucose excretion, declined with decrease in eGFR.

בסעיף **16 CLINICAL STUDIES**. עודכן המידע הבא:

[…]

16 CLINICAL STUDIES

Glycemic ~~control~~ Control in Patients with Type 2 Diabetes Mellitus

[…]

Heart Failure with Reduced Ejection Fraction

EMPEROR-Reduced (NCT03057977) was a randomized, double-blind, placebo-controlled study conducted in patients with chronic heart failure (New York Heart Association [NYHA] functional class II-IV) with reduced ejection fraction (left ventricular ejection fraction [LVEF] 40% or less) to evaluate the efficacy and safety of JARDIANCE 10 mg once daily, as adjunct to standard of care heart failure therapy.

Of 3730 patients, 1863 were randomized to JARDIANCE 10 mg and 1867 to placebo and were followed for a median of 16 months. The mean age of the study population was 67 years (range: 25 to 94 years) and 76% were men, 24% were women, and 27% were 75 years of age or older. Approximately 71% of the study population were White, 18% Asian and 7% Black or African American. At baseline, 50% of the patients had type 2 diabetes mellitus.

At randomization, 75% of patients were NYHA class II, 24% were class III and 0.5% were class IV. The mean LVEF was 28%. At baseline, the mean eGFR was 62 mL/min/1.73 m^2 and the median urinary albumin to creatinine ratio (UACR) was 22 mg/g. Approximately half of the patients (52%) had eGFR ≥60 mL/min/1.73 m^2, 24% had eGFR 45 to <60 mL/min/1.73 m^2, 19% had eGFR 30 to <45 mL/min/1.73 m^2 and 5% had eGFR 20 to <30 ml/min/1.73 m^2.

At baseline, 88% of patients were treated with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), or angiotensin receptor-neprilysin inhibitors (ARNI), 95% with beta-blockers, 71% with mineralocorticoid receptor antagonists (MRA), and 95% with diuretics.

The primary endpoint was the time to first event of either cardiovascular death (CV) or hospitalization for heart failure (HHF). Occurrence of HHF (first and recurrent) was assessed as a key secondary endpoint.

JARDIANCE was superior in reducing the risk of the primary composite endpoint of cardiovascular death or hospitalization for heart failure compared with placebo, mostly through a reduction in hospitalization for

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heart failure. JARDIANCE significantly reduced the risk of occurrence of HHF (first and recurrent) (see Table 14 and Figures 7 and 8).

Table 14 Treatment Effect for the Primary Composite Endpoint, its Components, and Key Secondary Endpoints

	Placebo N=1867	JARDIANCE 10 mg N=1863	Hazard ratio vs placebo (95% CI)	p-value
	Number of Patients (%)			
Primary composite of cardiovascular death or hospitalization for heart failure (time to first event)	462 (24.7%)	361 (19.4%)	0.75 (0.65-0.86)	<0.0001
Cardiovascular death[a,b]	202 (10.8%)	187 (10.0%)	0.92 (0.75, 1.12)	
Hospitalization for heart failure[a]	342 (18.3%)	246 (13.2%)	0.69 (0.59, 0.81)	
	Number of Events			
Hospitalization for heart failure (first and recurrent)	553	388	0.70 (0.58, 0.85)	0.0003

[a]Time to first event
[b]Includes deaths following hospitalization

Figure 7 Time to First Occurrence of the Primary Composite Endpoint of Cardiovascular Death or Hospitalization for Heart Failure

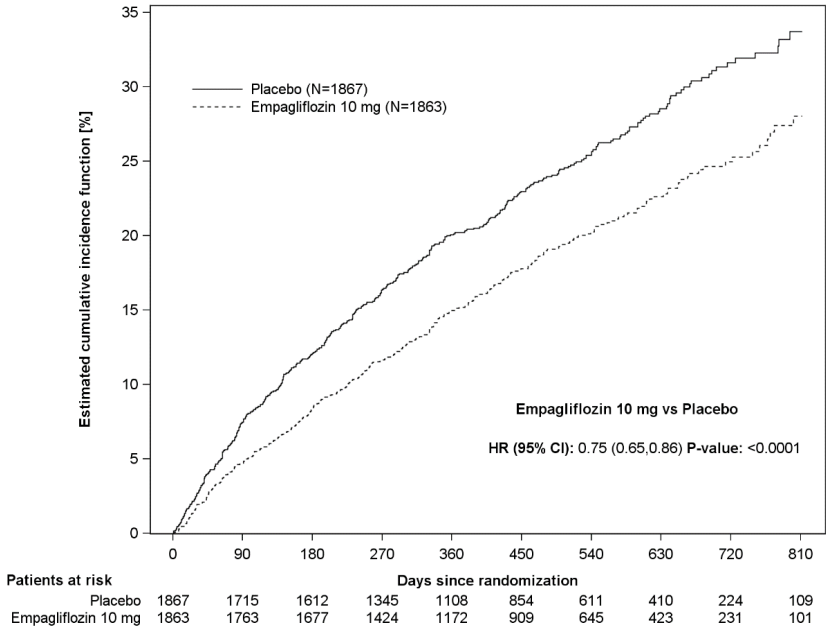

Figure 8 Time to Event of Hospitalization for Heart Failure (First and Recurrent)

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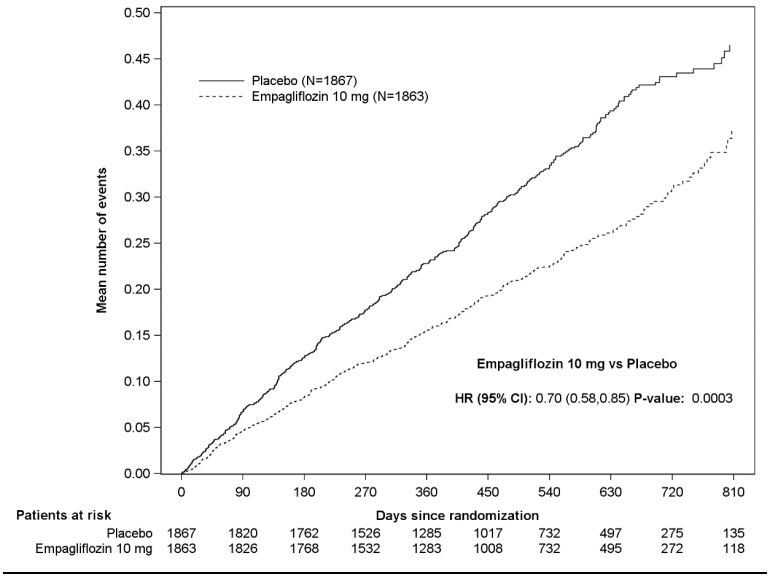
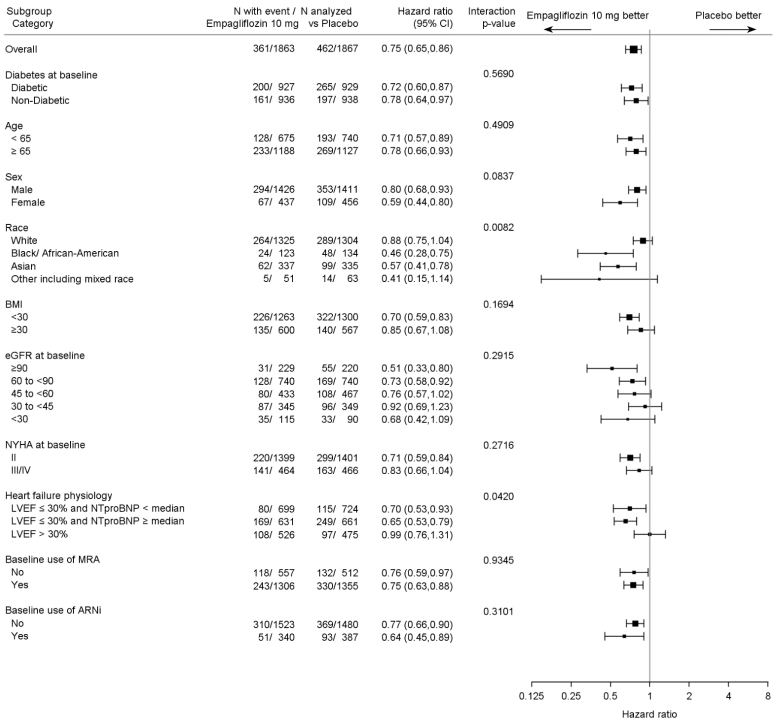


The results of the primary composite were generally consistent across the pre-specified subgroups, including heart failure patients with and without type 2 diabetes mellitus (see Figure 9).

Figure 9 Treatment Effects for the Primary Composite Endpoint (Cardiovascular Death and Hospitalization for Heart Failure) Subgroup Analysis (EMPEROR-Reduced)



LVEF >30%: Includes both above and below the median NTproBNP. To be eligible for inclusion, patients with an LVEF >30% were required to meet a higher NTproBNP threshold than those with LVEF ≤30%, unless they additionally had a history of HHF within the past 12 months.

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עדכונים מהותיים בעלון לצרכן

בסעיף **1. למה מיועדת התרופה** עודכן המידע הבא:

ג'ארדיאנס מיועדת:

- לשיפור השליטה ברמת הסוכר בדם במבוגרים עם סוכרת מסוג 2 בנוסף לדיאטה ופעילות גופנית.
- להפחתת הסיכון לתמותה ממחלת לב וכלי דם בחולים מבוגרים הסובלים מסוכרת מסוג 2 וממחלת לב וכלי דם קיימת .
- **ג'ארדיאנס 10 מ"ג** מיועדת להפחתת הסיכון לתמותה ממחלת לב וכלי דם ואשפוז כתוצאה מאי ספיקת לב במבוגרים עם אי ספיקת לב ומקטע פליטה ירוד.

ג'ארדיאנס אינה מיועדת לטיפול בסוכרת מסוג 1 או בחמצת קטוטית של סוכרת.(diabetic ketoacidosis)
ג'ארדיאנס לא מומלצת לשימוש לשיפור השליטה ברמת הסוכר במבוגרים עם סכרת מסוג 2 עם ערכי הערכת קצב סינון פקעית הכליה הקטנים מ- 30 ml/min/1.73m^2

בסעיף **2. לפני השימוש בתרופה** עודכן המידע הבא:

אין להשתמש בתרופה אם:

[...]

- אתה ~~סובל מאי-ספיקה כלייתית חמורה, מחלת כליות סופנית או~~ עובר טיפולי דיאליזה

בסעיף **3. כיצד תשתמש בתרופה** עודכן המידע הבא:

[...]

- המינון המקובל ההתחלתי בדרך כלל הוא טבלית ג'ארדיאנס 10 מ"ג פעם ביום- בבוקר עם או ללא אוכל הרופא יחליט האם להעלות את המינון לג'ארדיאנס 25 מ"ג.

[...]

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