יולי 2023

רופא/ה נכבד/ה
רוקח/ת נכבד/ה שלום רב,

<u>פרסום עדכון בעלוני התכשיר:</u>

<u>Forxiga film coated tablets 5 mg – 152-57-34012-00</u>

<u>Forxiga film coated tablets 10 mg – 152-58-34013-00</u>

חברת אסטרהזניקה ישראל מבקשת להודיע על עדכון עלון בהתאם להוראות משרד הבריאות בתאריך **יולי 2023.**

<u>הרכב:</u>

Dapagliflozin 5 mg

Dapagliflozin 10 mg

<u>התוויה:</u>

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 in adults for the treatment of symptomatic chronic heart failure.

Chronic kidney disease

Forxiga is indicated 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.

העדכונים המהותיים בעלון לרופא הינם:

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 in adults for the treatment of symptomatic chronic heart failure.

~~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 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.

4.4 Special warnings and precautions for use

General

Dapagliflozin should not be used in patients with type 1 diabetes mellitus (see "Diabetic ketoacidosis" in section 4.4).

…

Infiltrative cardiomyopathy
Patients with infiltrative cardiomyopathy have not been studied.

4.8 Undesirable effects

…

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 m². In the dapagliflozin cardiovascular outcome study in patients with heart failure with left ventricular ejection fraction > 40% (DELIVER), 3,126 patients were treated with dapagliflozin 10 mg and 3,127 patients with placebo for a median exposure time of 27 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, and patients with eGFR ≥ 25 mL/min/1.73 m².

…

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 one 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 DELIVER study, one (< 0.1%) patient in each treatment group reported a serious adverse event of genital infections. There were 3 (0.1%) patients with adverse events leading to discontinuations due to genital infection in the dapagliflozin group and none in the placebo group.

…

Hypoglycaemia

…

In the DAPA-HF study, major events of hypoglycaemia were reported in 4 (0.2%) patients in both the dapagliflozin and placebo treatment groups. . In the DELIVER study, major events of hypoglycaemia were reported in 6 (0.2%) patients in the dapagliflozin group and 7 (0.2%) in the placebo group. Major events of hypoglycaemia were ~~and~~ only observed ~~only~~ in patients with type 2 diabetes mellitus.

…

Volume depletion

…

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 DELIVER study, the numbers of patients with serious events of symptoms suggestive of volume depletion were 35 (1.1%) in the dapagliflozin group and 31 (1.0%) in the placebo group.

…

Diabetic ketoacidosis in type 2 diabetes mellitus

…

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

Urinary tract infections

…

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 discontinuations due to urinary tract~~tk~~ infections in each of the dapagliflozin and placebo groups. In the DELIVER study the numbers of patients with serious adverse events of urinary tract infections were 41 (1.3%) in the dapagliflozin group and 37 (1.2%) in the placebo group. There were 13 (0.4%) patients with adverse events leading to discontinuations due to urinary tract infections in the dapagliflozin group and 9 (0.3%) in the placebo group.

…

Increased creatinine

…

In the DAPA-HF and DELIVER stud~~y~~ies ,eGFR decreased over time in both the dapagliflozin group and the placebo group. In DAPA-HF, ~~T~~the initial decrease in mean eGFR was -4.3 mL/min/1.73 m² in the dapagliflozin group and -1.1 mL/min/1.73 m² in the placebo group. At 20 months, change from baseline in eGFR was similar between the treatment groups: -5.3 mL/min/1.73 m² for dapagliflozin and -4.5 mL/min/1.73 m² for placebo. In DELIVER, the decrease in mean eGFR at one month was -3.7 mL/min/1.73 m² in the dapagliflozin group and -0.4 mL/min/1.73 m² in the placebo group. At 24 months, change from baseline in eGFR was similar between treatment groups: -4.2 mL/min/1.73 m² in the dapagliflozin group and -3.2 mL/min/1.73 m² in the placebo group.

5.1 Pharmacodynamic properties

Mechanism of action

…

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 diastolic function, 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 glucose lowering effect and not limited to patients with diabetes as demonstrated in the DAPA-HF, DELIVER and DAPA-CKD studies. Other effects include an increase in haematocrit and reduction in body weight.

…

Heart Failure ~~with Reduced Ejection Fraction~~

DAPA-HF study: Heart failure with reduced ejection fraction (LVEF ≤ 40%)

Dapagliflozin And Prevention of Adverse outcomes in Heart Failure (DAPA-HF~~;~~ ~~NCT03036124~~) was an international, ~~multicenter~~multicentre, 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~~ effect of dapagliflozin compared with placebo, when added to background standard of care therapy, on the incidence of cardiovascular death and worsening heart failure.

Of 4,744 patients, 2,373 were randomi~~s~~zed to dapagliflozin~~FORXIGA~~ 10 mg and 2,371 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~~67.5% of the patients were classified as NYHA class II, ~~32~~31.6% class III, and ~~1~~0.9% class IV; median LVEF was 32%~~,~~ 56% of the heart failures were ischaemic, 36% were non-ischaemic and 8% were of unknown aetiology. In each treatment group, 42% of the patients had a ~~H~~history of type 2 diabetes mellitus ~~was present in 42%~~, and an additional 3% ~~had~~ of the patients in each group were classified as having type 2 diabetes mellitus based on a HbA1c ≥6.5% at both ~~enrollment~~enrolment and randomi~~s~~zation. Patients were on standard of care therapy; 94% of patients were treated with ACE-I ~~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 (with defibrillator function).

Patients with eGFR ≥ 30 mL/min/1.73 m² at enrolment were included in the study. The mean eGFR was 66 mL/min/1.73 m², 41% of patients had eGFR < 60mL/min/1.73 m² and 15% had eGFR < 45 mL/min/1.73 m².

Cardiovascular death and worsening heart failure

Dapagliflozin was superior to placebo in preventing the primary composite endpoint of cardiovascular~~CV~~ death, hospitali~~s~~zation 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~~ The effect~~. The FORXIGA and placebo event curves separated~~ was observed early and ~~continued to diverge over~~ was sustained throughout the duration of the study (Figure 3)~~. period (Table 11, Figures 3A, 3B and 3C).~~

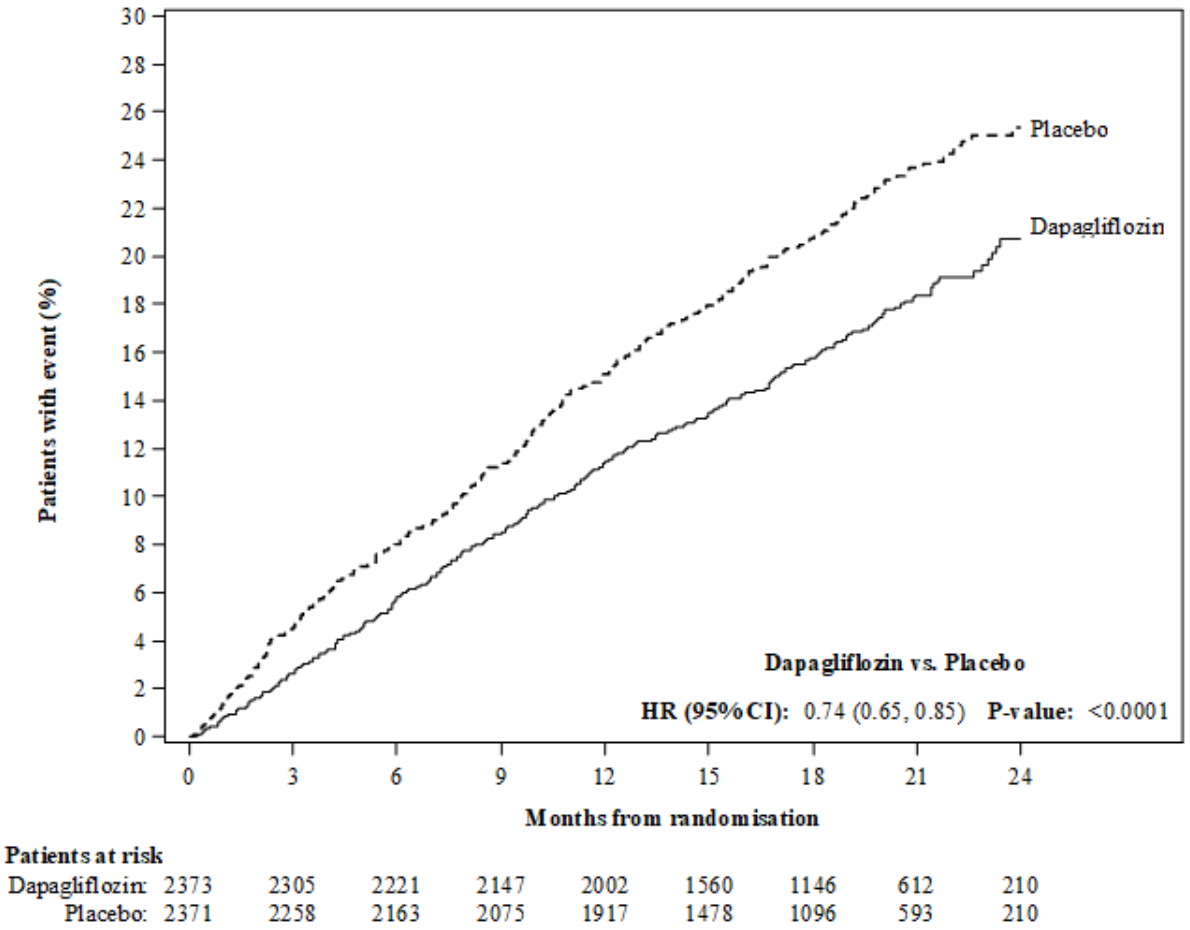
~~Table 11: Treatment Effect for the Primary Composite Endpoint*, its Components* and All-Cause Mortality in the DAPA-HF Study~~

	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)	
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 3: Kaplan-Meier Curves for the Primary Composite Endpoint (A), Cardiovascular Death (B), and Heart Failure Hospitalization (C) (DAPA-HF Study)

Figure 3A. Time to the First Occurrence of the Composite of cCardiovascular dDeath, HHospitalisszation for hHeart fFailure or uUrgent hHeart fFailure vVisit



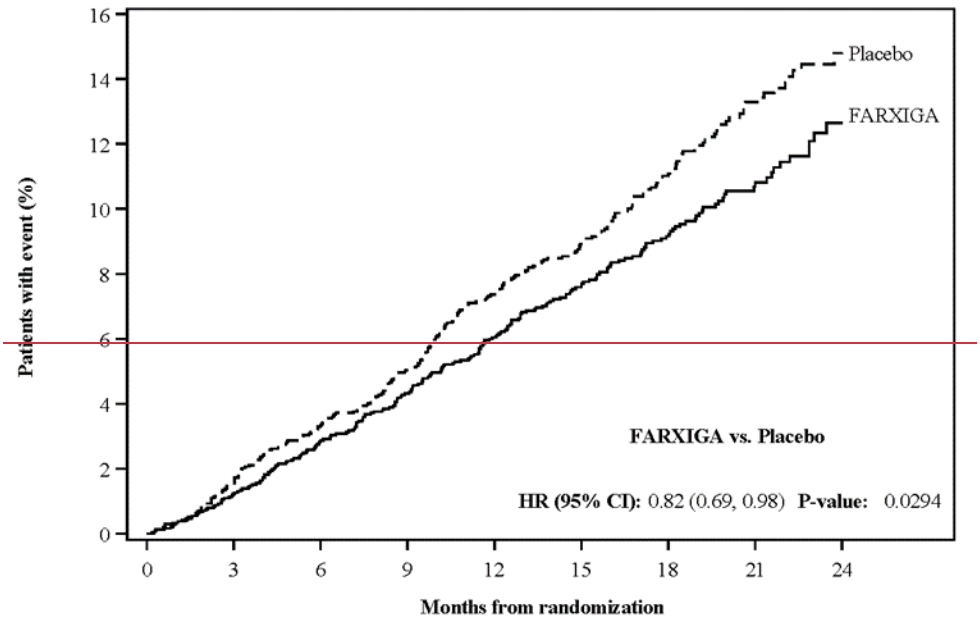
An urgent heart failure visit was defined as an urgent, unplanned, assessment by a physician, e.g. in an Emergency Department, and requiring treatment for worsening heart failure (other than just an increase in oral diuretics).
Patients at risk is the number of patients at risk at the beginning of the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

All three components of the primary composite endpoint individually contributed to the treatment effect (Figure 4). There were few urgent heart failure visits.

~~HR=Hazard ratio, CI=Confidence interval.~~

~~Figure 3B. Time to the First Occurrence of Cardiovascular Death~~

אסטרהזניקה (ישראל) בע"מ, רח' עתירי ידע 1 כפר סבא 4464301
טלפון 073-2226099 פקס 09-7406527

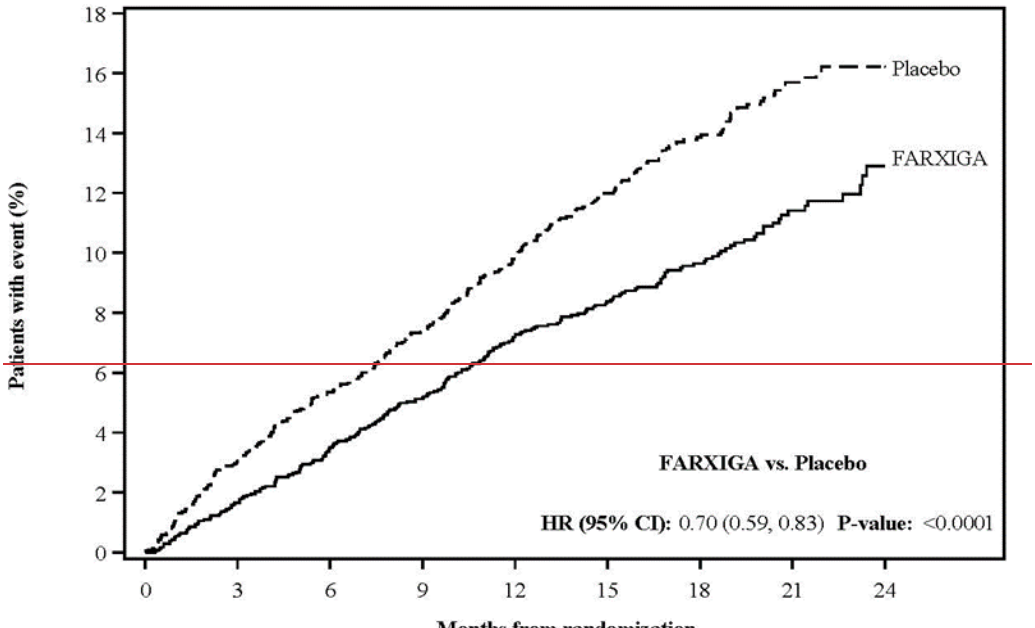


Patients at risk

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 3C: 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

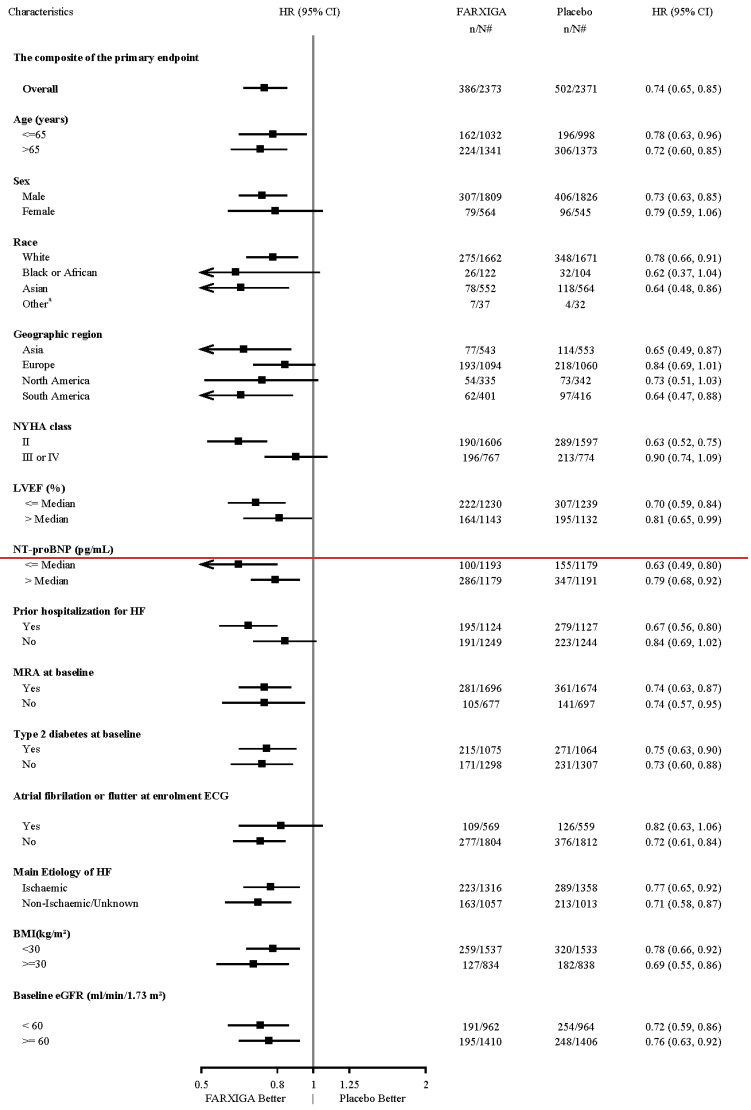
אסטרהזניקה (ישראל) בע"מ, רח' עתירי ידע 1 כפר סבא 4464301
טלפון 073-2226099 פקס 09-7406527

~~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 4).~~

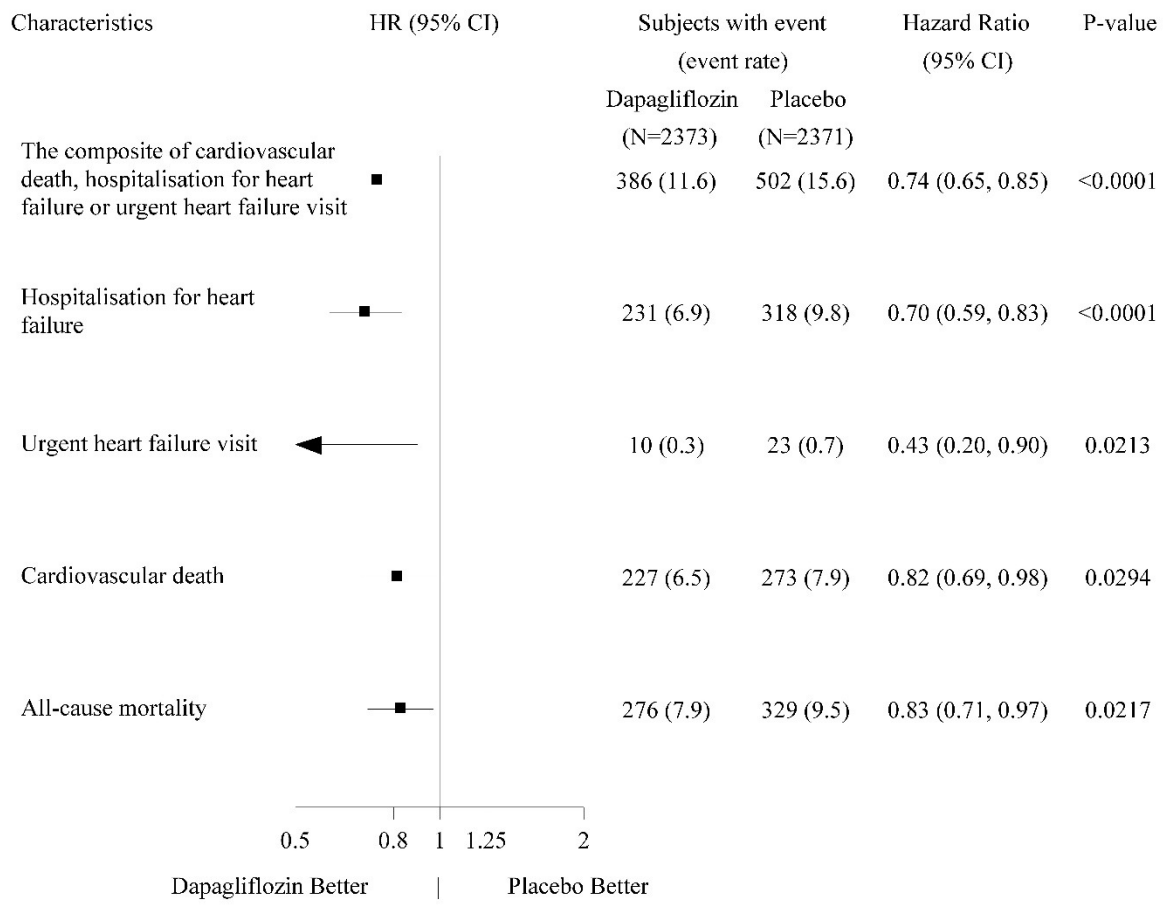
~~Figure 4. Treatment Effects for Primary Composite Endpoint(Cardiovascular Death and Heart Failure Events) Subgroup Analysis (DAPA-HF Study)~~



אסטרהזניקה (ישראל) בע"מ, רח' עתירי ידע 1 כפר סבא 4464301

טלפון 073-2226099 פקס 09-7406527

Figure 4: Treatment effects for the primary composite endpoint, its components and all-cause mortality



~~[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.~~

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).
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.
p-values for single components and all-cause mortality are nominal.

Dapagliflozin also reduced the total number of events of hospitalisations for heart failure (first and recurrent) and cardiovascular death; there were 567 events in the dapagliflozin group versus 742 events in the placebo group (Rate Ratio 0.75 [95% CI 0.65, 0.88]; p=0.0002).

אסטרהזניקה (ישראל) בע"מ, רח' עתירי ידע 1 כפר סבא 4464301
טלפון 073-2226099 פקס 09-7406527

The treatment benefit of dapagliflozin was observed in heart failure patients both with type 2 diabetes mellitus and without diabetes. Dapagliflozin reduced the primary composite endpoint of incidence of cardiovascular death and worsening heart failure with a HR of 0.75 (95% CI 0.63, 0.90) in patients with diabetes and 0.73 (95% CI 0.60, 0.88) in patients without diabetes.

The treatment benefit of dapagliflozin over placebo on the primary endpoint was also consistent across other key subgroups, including concomitant heart failure therapy, renal function (eGFR), age, gender, and region.

Patient reported outcome – heart failure symptoms

The treatment effect of dapagliflozin on heart failure symptoms was assessed by the Total Symptom Score of the Kansas City Cardiomyopathy Questionnaire (KCCQ-TSS), which quantifies heart failure symptom frequency and severity, including fatigue, peripheral oedema, dyspnoea and orthopnoea. The score ranges from 0 to 100, with higher scores representing better health status.

Treatment with dapagliflozin resulted in a statistically significant and clinically meaningful benefit over placebo in heart failure symptoms, as measured by change from baseline at month 8 in the KCCQ-TSS, (Win Ratio 1.18 [95% CI 1.11, 1.26]; $p < 0.0001$). Both symptom frequency and symptom burden contributed to the results. Benefit was seen both in improving heart failure symptoms and in preventing deterioration of heart failure symptoms.

In responder analyses, the proportion of patients with a clinically meaningful improvement on the KCCQ-TSS from baseline at 8 months, defined as 5 points or more, was higher for the dapagliflozin treatment group compared with placebo. The proportion of patients with a clinically meaningful deterioration, defined as 5 points or more, was lower for the dapagliflozin treatment group compared to placebo. The benefits observed with dapagliflozin remained when applying more conservative cut-offs for larger clinically meaningful change (Table 11).

Table 11. Number and percent of patients with clinically meaningful improvement and deterioration on the KCCQ-TSS at 8 months

Change from baseline at 8 months:	Dapagliflozin 10 mg n[a]=2086	Placebo n[a]=2062		
Improvement	n (%) improved[b]	n (%) improved[b]	Odds ratio[c] (95% CI)	p-value[f]
≥ 5 points	933 (44.7)	794 (38.5)	1.14 (1.06, 1.22)	0.0002
≥ 10 points	689 (33.0)	579 (28.1)	1.13 (1.05, 1.22)	0.0018
≥ 15 points	474 (22.7)	406 (19.7)	1.10 (1.01, 1.19)	0.0300
Deterioration	n (%) deteriorated[d]	n (%) deteriorated[d]	Odds ratio[e] (95% CI)	p-value[f]

≥ 5 points	537 (25.7)	693 (33.6)	0.84 (0.78, 0.89)	<0.0001
≥ 10 points	395 (18.9)	506 (24.5)	0.85 (0.79, 0.92)	<0.0001

[a] Number of patients with an observed KCCQ-TSS or who died prior to 8 months.
[b] Number of patients who had an observed improvement of at least 5, 10 or 15 points from baseline. Patients who died prior to the given timepoint are counted as not improved.
[c] For improvement, an odds ratio > 1 favours dapagliflozin 10 mg.
[d] Number of patients who had an observed deterioration of at least 5 or 10 points from baseline. Patients who died prior to the given timepoint are counted as deteriorated.
[e] For deterioration, an odds ratio < 1 favours dapagliflozin 10 mg.
[f] p-values are nominal.

Nephropathy

There were few events of the renal composite endpoint (confirmed sustained ≥ 50% eGFR decrease, ESKD, or renal death); the incidence was 1.2% in the dapagliflozin group and 1.6% in the placebo group.

DELIVER study: Heart failure with left ventricular ejection fraction > 40%

Dapagliflozin Evaluation to Improve the LIVEs of Patients with PReserved Ejection Fraction Heart Failure (DELIVER) was an international, multicentre, randomised, double-blind, placebo-controlled study in patients aged ≥ 40 years with heart failure (NYHA class II-IV) with LVEF > 40% and evidence of structural heart disease, to determine the effect of dapagliflozin compared with placebo on the incidence of cardiovascular death and worsening heart failure.

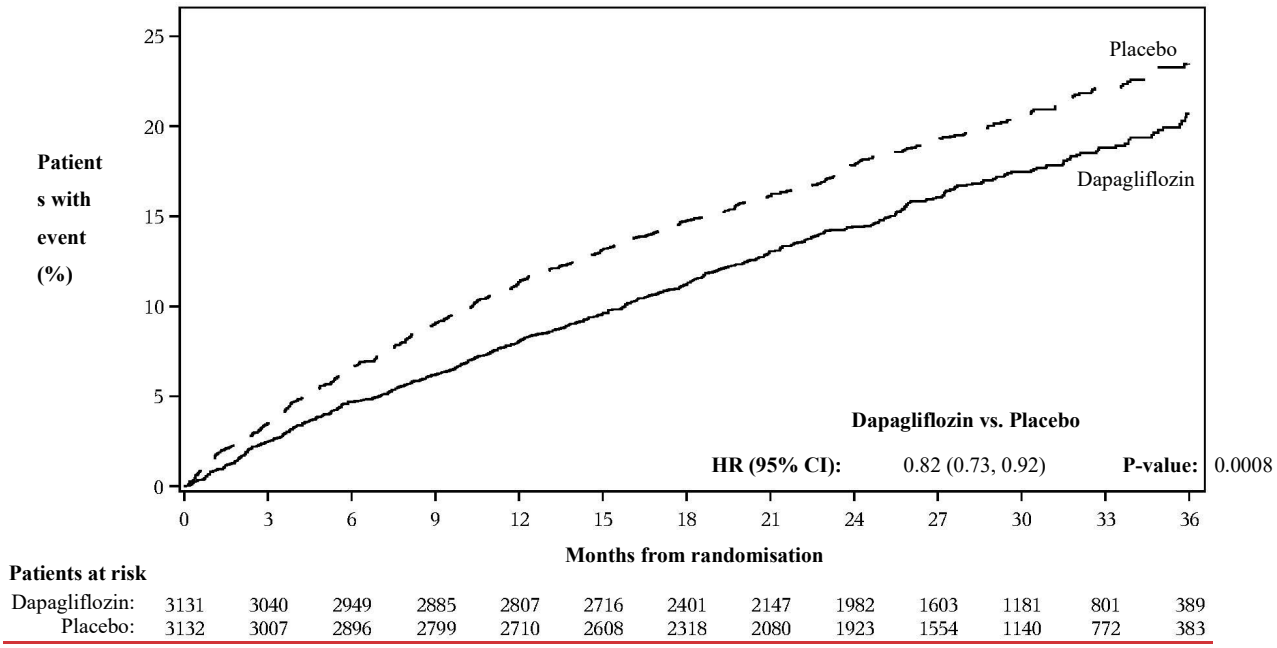
Of 6,263 patients, 3,131 were randomised to dapagliflozin 10 mg and 3,132 to placebo and followed for a median of 28 months. The study included 654 (10%) subacute heart failure patients (defined as randomised during hospitalisation for heart failure or within 30 days of discharge). The mean age of the study population was 72 years and 56% were male.

At baseline, 75% patients were classified as NYHA class II, 24% class III and 0.3% class IV. Median LVEF was 54%, 34% of the patients had LVEF ≤ 49%, 36% had LVEF 50-59% and 30% had LVEF ≥ 60%. In each treatment group, 45% had a history of type 2 diabetes mellitus. Baseline therapy included ACEi/ARB/ARNI (77%), beta-blockers (83%) diuretics (98%) and MRA (43%).

The mean eGFR was 61 mL/min/1.73 m², 49% of patients had eGFR < 60mL/min/1.73 m², 23% had eGFR < 45 mL/min/1.73 m², and 3% had eGFR < 30 mL/min/1.73 m².

Dapagliflozin was superior to placebo in reducing the incidence of the primary composite endpoint of cardiovascular death, hospitalisation for heart failure or urgent heart failure visit (HR 0.82 [95% CI 0.73, 0.92]; p=0.0008) (Figure 5).

Figure 5: Time to first occurrence of the composite of cardiovascular death, hospitalisation for heart failure or urgent heart failure visit



Patients at risk

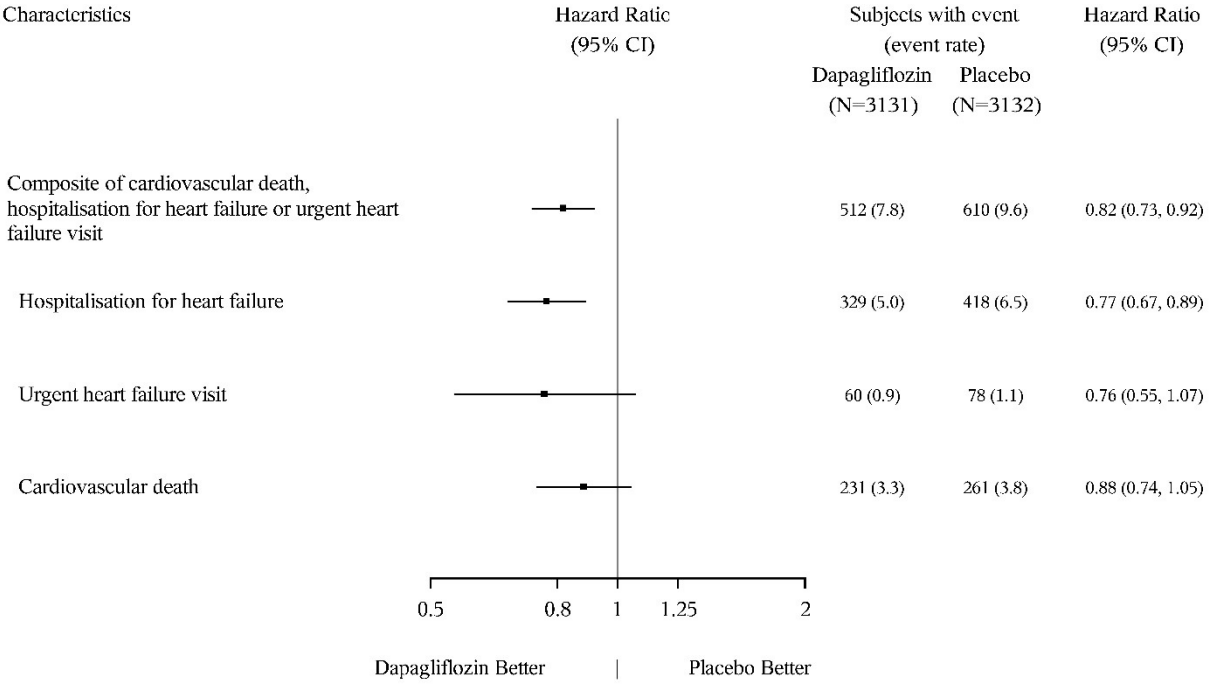
Dapagliflozin:	3131	3040	2949	2885	2807	2716	2401	2147	1982	1603	1181	801	389
Placebo:	3132	3007	2896	2799	2710	2608	2318	2080	1923	1554	1140	772	383

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.

Figure 6 presents the contribution of the three components of the primary composite endpoint to the treatment effect.

Figure 6: Treatment effects for the primary composite endpoint and its components



אסטרהזניקה (ישראל) בע"מ, רח' עתירי ידע 1 כפר סבא 4464301

טלפון 073-2226099 פקס 09-7406527

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).
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.
Cardiovascular death, here presented as a component of the primary endpoint, was also tested under formal Type 1 error control as a secondary endpoint.

Dapagliflozin was superior to placebo in reducing the total number of heart failure events (defined as first and recurrent hospitalisation for heart failure or urgent heart failure visits) and cardiovascular death; there were 815 events in the dapagliflozin group versus 1057 events in the placebo group (Rate Ratio 0.77 [95% CI 0.67, 0.89]; p=0.0003).

The treatment benefit of dapagliflozin over placebo on the primary endpoint was observed across subgroups of patients with LVEF ≤ 49%, 50–59%, and ≥ 60%. Effects were also consistent across other key subgroups categorised by e.g. age, gender, NYHA class, NT-proBNP level, subacute status, and type 2 diabetes mellitus status.

Patient reported outcome – heart failure symptoms

Treatment with dapagliflozin resulted in a statistically significant benefit over placebo in heart failure symptoms, as measured by change from baseline at month 8 in the KCCQ-TSS, (Win Ratio 1.11 [95% CI 1.03, 1.21]; p=0.0086). Both symptom frequency and symptom burden contributed to the results.

In responder analyses, the proportion of patients who experienced a moderate (≥ 5 points) or large (≥ 14 points) deterioration on the KCCQ-TSS from baseline at 8 months was lower in the dapagliflozin treatment group; 24.1% of patients on dapagliflozin versus 29.1% on placebo experienced a moderate deterioration (Odds Ratio 0.78 [95% CI 0.64, 0.95]) and 13.5% of patients on dapagliflozin versus 18.4% on placebo experienced a large deterioration (Odds Ratio 0.70 [95% CI 0.55, 0.88]). The proportion of patients with a small to moderate improvement (≥ 13 points) or a large improvement (≥ 17 points) did not differ between treatment groups.

Heart failure across DAPA-HF and DELIVER studies

In a pooled analysis of DAPA-HF and DELIVER, the HR for dapagliflozin versus placebo on the composite endpoint of cardiovascular death, hospitalisation for heart failure or urgent heart failure visit was 0.78 (95% CI 0.72, 0.85), p < 0.0001. The treatment effect was consistent across the LVEF range, without attenuation of effect by LVEF.

In a pre-specified subject level pooled analysis of the DAPA-HF and DELIVER studies, dapagliflozin compared with placebo reduced the risk of cardiovascular death (HR 0.85 [95% CI 0.75, 0.96], p=0.0115). Both studies contributed to the effect.

…

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% ~~were 45%, 100% and 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 haemodialysis on dapagliflozin exposure is not known. The effect of reduced renal function on systemic exposure was evaluated in a population pharmacokinetic model. Consistent with previous results, model predicted AUC was higher in patients with chronic kidney disease compared with patients with normal renal function, and was not meaningfully different in chronic kidney disease patients with type 2 diabetes mellitus and without diabetes.

…

Revised on ~~September~~ July ~~2022~~2023

עדכונים מהותיים בעלון לצרכן:

1. למה מיועדת התרופה?

סוכרת מסוג 2

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.

אי ספיקת לב

פורסיגה ניתנת לטיפול ב~~ל~~מבוגרים ~~לטיפול~~ באי ספיקת לב כרונית סימפטומטית. ~~כטיפול להורדת הסיכון למוות קרדיווסקולרי ולאשפוז כתוצאה מאי ספיקת לב במבוגרים עם אי ספיקת לב (NYHA class II-IV) עם מקטע פליטה ירוד.~~

מחלת כליות כרונית

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

2. לפני השימוש בתרופה

…

לפני הטיפול בפורסיגה ספר לרופא, לרוקח או לאחות אם:

- הנך סובל מסוכרת מסוג 1 (סוג של סוכרת בה הגוף אינו מייצר אינסולין). פורסיגה אינה מיועדת לטיפול בסוכרת מסוג 1.
- הנך עומד לעבור ניתוח.
- כמות המזון שאתה אוכל קטנה יותר בשל מחלה, בשל ביצוע ניתוח או שהנך שומר על דיאטה.
- הנך שותה אלכוהול לעיתים תכופות מאוד, או שהנך שותה כמות גדולה של אלכוהול בזמן קצר.
- אם הנך סובל מסוכרת והנך מפתח אחד מהסימנים הבאים, שיכול להיות סימן לחמצת קטוטית סוכרתית (Diabetic ketoacidosis) ~~קטואצידוזיס~~: בחילה, הקאה, כאבים באזור הבטן, צמאון מוגבר, ישנוניות יוצאת דופן או עייפות, נשימה מאומצת, קשיי נשימה, איבוד תאבון, ירידה מהירה במשקל, בלבול, ריח אציטון בנשימה, טעם אופייני בפה ושינוי ריח שתן/זיעה. אם הנך חש באחד מסימנים אלו הפסק את השימוש בתרופה ופנה באופן מיידי לרופא או פנה לבית חולים קרוב באופן מיידי.
- נמצאו בבדיקות רמות גבוהות של קטונים בשתן או בדם. זהו סימן של חמצת קטוטית סוכרתית (Diabetic ketoacidosis) ~~קטואצידוזיס סוכרתי~~, בעיה נדירה ולעיתים מסכנת חיים שיכולה להיות כתוצאה מסוכרת. גורמי סיכון לחמצת קטוטית סוכרתית (Diabetic ketoacidosis) ~~קטואצידוזיס~~: צום ממושך, הפחתה פתאומית ~~של~~ במינון האינסולין או דרישה מוגברת לאינסולין עקב מחלה ~~אקוטית~~חמורה, ~~ירידה בצריכה הקלורית עקב מחלה~~ או ניתוח, התייבשות, ~~מחלות לבלב שמקושרות לחוסר באינסולין (כגון סוכרת סוג 1, היסטוריה של דלקות בלבלב או ניתוחים)~~ וצריכת אלכוהול מוזגמת.
- אם הנך מטופל בפורסיגה, חמצת קטוטית סוכרתית (Diabetic ketoacidosis) עשויה לקרות גם אם רמת הסוכר בדם שלך תקינה.

...

נערך ~~בספטמבר~~ ביולי 2022~~3~~ 2023 בהתאם להנחיות משרד הבריאות.

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

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

בכבוד רב,

קארין קנבל דובסון
רוקחת ממונה
אסטרהזניקה (ישראל) בע"מ