פברואר 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.

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.

חברת אסטרהזניקה ישראל מבקשת להודיע על עדכון עלון בהתאם להוראות משרד הבריאות בתאריך **ספטמבר ודצמבר 2019.**

העדכון המהותי בעלון לרופא הוא:

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- as ~~M~~monotherapy when ~~diet and exercise alone do not provide adequate glycaemic control in patients for whom use of~~ metformin is considered inappropriate due to intolerance.
- in addition to other medicinal products for the treatment of type 2 diabetes.

~~Add-on combination therapy~~

~~In combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations).~~

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.

4.2 Posology and method of administration

Posology

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

The recommended dose is 10 mg dapagliflozin once daily ~~for monotherapy and add-on combination therapy with other glucose-lowering medicinal products including insulin.~~

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). ~~Due to the limited therapeutic experience in patients 75 years and older, initiation of dapagliflozin therapy is not recommended.~~

4.4 Special warnings and precautions for use

Use in patients at risk for volume depletion **and/or** hypotension ~~and/or electrolyte imbalances~~

Due to its mechanism of action, dapagliflozin increases diuresis ~~associated with a~~ which may lead to the modest decrease in blood pressure observed in clinical studies (see section 5.1)~~ which~~It may be more pronounced in patients with very high blood glucose concentrations.

~~Dapagliflozin is not recommended for use in patients receiving loop diuretics (see section 4.5) or who are volume depleted, e.g. due to acute illness (such as gastrointestinal illness).~~

Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as ~~patients with known cardiovascular disease,~~ patients on anti-hypertensive therapy with a history of hypotension or elderly patients.

~~For patients receiving dapagliflozin, i~~ In case of intercurrent conditions that may lead to volume depletion (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit~~)~~ and electrolytes) is recommended. Temporary interruption of treatment with dapagliflozin is

recommended for patients who develop volume depletion until the depletion is corrected (see section 4.8).

Necrotising fasciitis of the perineum (Fournier's gangrene)

Post-marketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors (see section 4.8). This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Forxiga should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Urinary tract infections

~~Urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to placebo in a pooled analysis up to 24 weeks (see section 4.8). Pyelonephritis was uncommon and occurred at a similar frequency to control.~~ Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of dapagliflozin should be considered when treating pyelonephritis, urosepsis ~~or severe urinary tract infections. Consider risk to benefit in patient with history of recurrent urinary tract infections. Patients should be advised of an increased risk of urinary tract infections (see section 4.8).~~

~~Urosepsis and Pyelonephritis~~

~~There have been post-marketing reports of serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization in patients receiving SGLT2 inhibitors, including FORXIGA.~~

~~Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated (see section 4.8).~~

Elderly patients (≥ 65 years)

Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics.

~~In subjects ≥ 65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse reactions related to renal impairment or failure compared with placebo. The most commonly reported adverse reaction related to renal function was serum creatinine increases, the majority of which were transient and reversible (see section 4.8).~~

Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics. In subjects ≥ 65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse reactions related to volume depletion (see section 4.8).

Therapeutic experience in patients 75 years and older is limited. Initiation of dapagliflozin therapy in this population is not recommended (see sections 4.2 and 5.2).

Cardiac failure

Experience in NYHA class I-II is limited, and tThere is no experience in clinical studies with dapagliflozin in NYHA class III–IV.

Use in patients treated with pioglitazone

While a causal relationship between dapagliflozin and bladder cancer is unlikely (see sections 4.8 and 5.3), as a precautionary measure, dapagliflozin is not recommended for use in patients concomitantly treated with pioglitazone. Available epidemiological data for pioglitazone suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone.

Elevated haematocrit

Haematocrit increase was observed with dapagliflozin treatment (see section 4.8); therefore, caution in patients with already elevated haematocrit is warranted.

Fournier’s gangrene

There are few reports of necrotizing fasciitis / Fournier’s gangrene in patients taking SGLT-2 inhibitors.

There is a difficulty to assess the Correlation between Fournier’s gangrene to FORXIGA since Obesity and diabetes are risk factors for developing Fournier's gangrene.

the symptoms of this infection include: tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum and have a fever above 38 °C or a general feeling of being unwell.

Health care professionals should assess patients for Fournier’s gangrene if they present with the symptoms described above. If suspected, start treatment immediately. Discontinue the SGLT2 inhibitor, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

4.8 Undesirable effects

Summary of the safety profile

In the clinical studies in type 2 diabetes, more than 15,000 patients have been treated with dapagliflozin.

The primary assessment of safety and tolerability was conducted in a pre-specified pooled analysis of 13 short-term (up to 24 weeks) placebo-controlled studies with 2,360 subjects ~~were~~ treated with dapagliflozin 10 mg and 2,295 ~~were~~ treated with placebo.

In the dapagliflozin cardiovascular outcomes study (see section 5.1), 8,574 patients received dapagliflozin 10 mg and 8,569 received placebo for a median exposure time of 48 months. In total, there were 30,623 patient-years of exposure to dapagliflozin.

The most frequently reported adverse reactions across the clinical studies were genital infections. ~~was hypoglycaemia, which depended on the type of background therapy used in each study. The frequency of minor episodes of hypoglycaemia was similar between treatment groups, including placebo, with the exceptions of studies with add-on sulphonylurea (SU) and add-on insulin therapies. Combination therapies with sulphonylurea and add-on insulin had higher rates of hypoglycaemia (see *Hypoglycaemia* below).~~

Tabulated list of adverse reactions

The following adverse reactions have been identified in the placebo-controlled clinical trials. 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 1. Adverse reactions in placebo-controlled studies[a]

System organ class	**Very common**	**Common***	**Uncommon****	**Rare**	**Very rare**
Infections and infestations		Vulvovaginitis, balanitis and related genital infections *[b,c] Urinary tract infection*[b,d]	Fungal infection**		Necrotising fasciitis of the perineum (Fournier's gangrene)[b,i]
Metabolism and	Hypoglycaemia		Volume	Diabetic	

nutrition disorders	(when used with SU or insulin) [b]		depletion [b,e] Thirst**	ketoacidosis[i]	
Nervous system disorders		Dizziness			
Gastrointestinal disorders			Constipation** Dry mouth**		
Skin and subcutaneous tissue disorders		Rash [j]			angioedema
Musculoskeletal and connective tissue disorders		Back pain*			
Renal and urinary disorders		Dysuria Polyuria*[,f]	Nocturia** ~~Renal impairment**[,b]~~		
Reproductive system and breast disorders			Vulvovaginal pruritus** Pruritus genital**		
Investigations		Haematocrit increased[g] Creatinine renal clearance decreased during initial treatment[b] Dyslipidaemia[h]	Blood creatinine increased during initial treatment**[,b] Blood urea increased** Weight decreased**		

[a]The table shows up to 24-week (short-term) data regardless of glycaemic rescue.

[b]See corresponding subsection below for additional information.

[c]Vulvovaginitis, balanitis and related genital infections includes, e.g. the predefined preferred terms: vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, vulval abscess.

[d]Urinary tract infection includes the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection and prostatitis.

[e]Volume depletion includes, e.g. the predefined preferred terms: dehydration, hypovolaemia, hypotension.

[f]Polyuria includes the preferred terms: pollakiuria, polyuria, urine output increased.

[g]Mean changes from baseline in haematocrit were 2.30 % for dapagliflozin 10 mg versus 0.33% for placebo. Haematocrit values >55% were reported in 1.3% of the subjects treated with dapagliflozin 10 mg versus 0.4% of placebo subjects.

[h]Mean percent change from baseline for dapagliflozin 10 mg versus placebo, respectively, was: total cholesterol 2.5% versus 0.0%; HDL cholesterol 6.0% versus 2.7%; LDL cholesterol 2.9% versus -1.0%; triglycerides –2.7% versus -0.7%.

iSee section 4.4

jAdverse reaction was identified through postmarketing surveillance. Rash includes the following preferred

terms, listed in order of frequency in clinical trials: rash, rash generalised, rash pruritic, rash macular, rash

maculo-papular, rash pustular, rash vesicular, and rash erythematous. In active- and placebo-controlled clinical trials (dapagliflozin, N=5936, All control, N=3403), the frequency of rash was similar for dapagliflozin (1.4%) and all control (1.4%), respectively.

[l]Reported in the cardiovascular outcomes study in patients with type 2 diabetes. Frequency is based on annual rate.

[*]Reported in ≥ 2% of subjects and ≥ 1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

[**]Reported by the investigator as possibly related, probably related or related to study treatment and reported in ≥ 0.2% of subjects and ≥ 0.1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

Description of selected adverse reactions

Vulvovaginitis, balanitis and related genital infections

In the 13-study safety pool, vulvovaginitis, balanitis and related genital infections were reported in 5.5% and 0.6% of subjects who received dapagliflozin 10 mg and placebo, respectively. Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females (8.4% and 1.2% for dapagliflozin and placebo, respectively), and subjects with a prior history were more likely to have a recurrent infection.

In the dapagliflozin cardiovascular outcomes study, the number of patients with serious adverse events of genital infections were few and balanced: 2 patients in each of the dapagliflozin and placebo groups.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Cases of Fournier's gangrene have been reported postmarketing in patients taking SGLT2 inhibitors, including dapagliflozin (see section 4.4).

In the dapagliflozin cardiovascular outcomes study with 17,160 type 2 diabetes mellitus patients and a median exposure time of 48 months, a total of 6 cases of Fournier's gangrene were reported, one in the dapagliflozin-treated group and 5 in the placebo group.

Hypoglycaemia

In the dapagliflozin cardiovascular outcomes 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.

Volume depletion

In the 13-study safety pool reactions suggestive of ~~related to~~ volume depletion (including, reports of dehydration, hypovolaemia or hypotension) were reported in 1.1% and 0.7% of subjects who received dapagliflozin 10 mg and placebo, respectively; serious reactions occurred in < 0.2% of subjects balanced between dapagliflozin 10 mg and placebo (see section 4.4).

In the dapagliflozin cardiovascular outcomes study, the numbers of patients with events suggestive of volume depletion were balanced between treatment groups: 213 (2.5%) and 207 (2.4%) in the dapagliflozin and placebo groups, respectively. Serious adverse events were reported in 81 (0.9%) and 70 (0.8%) in the dapagliflozin and placebo group, respectively. Events were generally balanced between treatment groups across subgroups of age, diuretic use, blood pressure and ACE-I/ARB use. In patients with eGFR < 60 mL/min/1.73 m^2 at baseline, there were 19 events of serious adverse events suggestive of volume depletion in the dapagliflozin group and 13 events in the placebo group.

Diabetic ketoacidosis

In the dapagliflozin cardiovascular outcomes study, with a median exposure time of 48 months, events of DKA were reported in 27 patients in the dapagliflozin 10 mg group and 12 patients in the placebo group. The events occurred evenly distributed over the study period. Of the 27 patients with DKA events in the dapagliflozin group, 22 had concomitant insulin treatment at the time of the

event. Precipitating factors for DKA were as expected in a type 2 diabetes mellitus population (see section 4.4).

Urinary tract infections

In the 13-study safety pool, urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to placebo (4.7% versus 3.5%, respectively; see section 4.4). Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females, and subjects with a prior history were more likely to have a recurrent infection.

In the dapagliflozin cardiovascular outcomes study, serious events of urinary tract infections were reported less frequently for dapagliflozin 10 mg compared with placebo, 79 (0.9%) events versus 109 (1.3%) events, respectively.

Increased creatinine

Adverse drug reactions related to increased creatinine were grouped (e.g. decreased renal creatinine clearance, renal impairment, increased blood creatinine and decreased glomerular filtration rate). This grouping of reactions was reported in 3.2% and 1.8% of patients who received dapagliflozin 10 mg and placebo, respectively. In patients with normal renal function or mild renal impairment (baseline eGFR ≥ 60 mL/min/1.73m2) this grouping of reactions were reported in 1.3% and 0.8% of patients who received dapagliflozin 10 mg and placebo, respectively. These reactions were more common in patients with baseline eGFR ≥ 30 and < 60 mL/min/1.73m2 (18.5% dapagliflozin 10 mg vs 9.3% placebo).

Further evaluation of patients who had renal-related adverse events showed that most had serum creatinine changes of ≤ 0.5 mg/dL from baseline. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment.

In the dapagliflozin cardiovascular outcomes study, including elderly patients and patients with renal impairment (eGFR less than 60 mL/min/1.73 m^2), eGFR decreased over time in both treatment groups. At 1 year, mean eGFR was slightly lower, and at 4 years, mean eGFR was slightly higher in the dapagliflozin group compared with the placebo group.

~~*Parathyroid hormone (PTH)*~~

~~Small increases in serum PTH levels were observed with increases being larger in subjects with higher baseline PTH concentrations. Bone mineral density measurements in patients with normal or mildly impaired renal function did not indicate bone loss over a treatment period of two years.~~

~~*Malignancies*~~

~~During clinical trials, the overall proportion of subjects with malignant or unspecified tumours was similar between those treated with dapagliflozin (1.50%) and placebo/comparator (1.50%), and there was no carcinogenicity or mutagenicity signal in animal data (see section 5.3). When considering the cases of tumours occurring in the different organ systems, the relative risk associated with dapagliflozin was above 1 for some tumours (bladder, prostate, breast) and below 1 for others (e.g. blood and lymphatic, ovary, renal tract), not resulting in an overall increased tumour risk associated with dapagliflozin. The increased/decreased risk was not statistically significant in any of the organ systems. Considering the lack of tumour findings in non-clinical studies as well as the short latency between first drug exposure and tumour diagnosis, a causal relationship is considered unlikely. Since the numerical imbalance of breast, bladder and prostate tumours must be considered with caution, it will be further investigated in post-authorisation studies.~~

~~Special populations~~

~~*Elderly (≥ 65 years)*~~

~~In subjects ≥ 65 years of age, adverse reactions related to renal impairment or failure were reported in 7.7% of subjects treated with dapagliflozin and 3.8% of subjects treated with placebo (see section 4.4). The most commonly reported adverse reaction related to renal function was increased serum creatinine. The majority of these reactions were transient and reversible. In subjects ≥ 65 years of age, adverse reactions of volume depletion, most commonly reported as hypotension, were reported in 1.7% and 0.8% of dapagliflozin-treated subjects and placebo-treated subjects, respectively (see section 4.4).~~

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacodynamic effects

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in subjects with type 2 diabetes mellitus following the administration of dapagliflozin. Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day) at a dapagliflozin dose of 10 mg/day in subjects with type 2 diabetes mellitus for 12 weeks. Evidence of sustained glucose excretion was seen in subjects with type 2 diabetes mellitus given dapagliflozin 10 mg/day for up to 2 years.

This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume in subjects with type 2 diabetes mellitus. Urinary volume increases in subjects with type 2 diabetes mellitus treated with dapagliflozin 10 mg were sustained at 12 weeks and amounted to approximately 375 ml/day. The increase in urinary volume was associated with a

small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations.

Urinary uric acid excretion was also increased transiently (for 3-7 days) and accompanied by a sustained reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations ranged from -48.3 to -18.3 micromoles/l (-0.87 to -0.33 mg/dl).

Clinical efficacy and safety

Both improvement of glycaemic control and reduction of cardiovascular and renal morbidity and mortality are an integral part of the treatment of type 2 diabetes.

Fourteen double-blind, randomised, controlled clinical trials were conducted with 7,056 subjects with type 2 diabetes to evaluate the glycaemic efficacy and safety of Forxiga; 4,737 subjects in these studies were treated with dapagliflozin. Twelve studies had a treatment period of 24 weeks duration, 8 with long-term extensions ranging from 24 to 80 weeks (up to a total study duration of 104 weeks), one study had a 28-week treatment period. and one study was 52 weeks in duration with long-term extensions of 52 and 104 weeks (total study duration of 208 weeks). Mean duration of diabetes ranged from 1.4 to 16.9 years. Fifty-two percent (50%) had mild renal impairment and 11% had moderate renal impairment. Fifty-one percent (51%) of the subjects were men, 84% were White, 8% were Asian, 3% were Black and 4% were of other racial groups. Eighty -one percent (81%) of the subjects had a body mass index (BMI) ≥ 27. Furthermore, two 12-week, placebo-controlled studies were conducted in patients with inadequately controlled type 2 diabetes and hypertension.

A cardiovascular outcome study (DECLARE) was conducted with dapagliflozin 10 mg compared with placebo in 17,160 patients with type 2 diabetes mellitus with or without established cardiovascular disease to evaluate the effect on cardiovascular and renal events.

~~*Cardiovascular safety*~~

~~A meta-analysis of cardiovascular events in the clinical program was performed. In the clinical program, 34.4% of subjects had a history of cardiovascular disease (excluding hypertension) at baseline and 67.9% had hypertension. Cardiovascular episodes were adjudicated by an independent adjudication committee. The primary end point was the time-to-first event of one of the following outcomes: cardiovascular death, stroke, myocardial infarction (MI) or hospitalisation for unstable angina. Primary episodes occurred at a rate of 1.62% per patient-year in subjects treated with dapagliflozin and 2.06% in comparator-treatment subjects, per patient-year. The hazard ratio comparing dapagliflozin to comparator was 0.79 (95% Confidence interval [CI]: 0.58, 1.07), indicating that in this analysis Forxiga is not associated with an increase in cardiovascular~~

~~risk in patients with type 2 diabetes mellitus. Cardiovascular death, MI and stroke were observed with a hazard ratio of 0.77 (95% CI: 0.54, 1.10).~~

Renal impairment

Moderate renal impairment (eGFR ≥ 30 to < 60 ml/min/1.73 m2)

The efficacy of dapagliflozin was also assessed separately in a dedicated study of diabetic subjects with moderate renal impairment (252 subjects with mean eGFR 45 ml/min/1.73 m2). The mean change from baseline in HbA1c at 24 weeks was -0.44% and -0.33%, for dapagliflozin 10 mg and placebo, respectively.

Patients with baseline HbA1c ≥ 9%

In a pre-specified analysis of subjects with baseline HbA1c ≥ 9.0%, treatment with dapagliflozin 10 mg resulted in statistically significant reductions in HbA1c at Week 24 as a monotherapy (adjusted mean change from baseline: - 2.04% and 0.19% for dapagliflozin 10 mg and placebo, respectively) and as an add-on to metformin (adjusted mean change from baseline: -1.32% and -0.53% for dapagliflozin and placebo, respectively).

Cardiovascular and renal outcomes

Dapagliflozin Effect on Cardiovascular Events (DECLARE) was an international, multicentre, randomised, double-blind, placebo-controlled clinical study conducted to determine the effect of dapagliflozin compared with placebo on cardiovascular outcomes when added to current background therapy. All patients had type 2 diabetes mellitus and either at least two additional cardiovascular risk factors (age ≥ 55 years in men or ≥ 60 years in women and one or more of dyslipidaemia, hypertension or current tobacco use) or established cardiovascular disease.

Of 17,160 randomised patients, 6,974 (40.6%) had established cardiovascular disease and 10,186 (59.4%) did not have established cardiovascular disease. 8,582 patients were randomised to dapagliflozin 10 mg and 8,578 to placebo and were followed for a median of 4.2 years.

The mean age of the study population was 63.9 years, 37.4% were female. In total, 22.4% had had diabetes for ≤ 5 years, mean duration of diabetes was 11.9 years. Mean HbA1c was 8.3% and mean BMI was 32.1 kg/m^2.

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 at baseline, 82.0% of the patients were being treated with metformin, 40.9% with insulin, 42.7% with a sulfonylurea, 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.

The primary endpoints were time to first event of the composite of cardiovascular death, myocardial infarction or ischaemic stroke (MACE) and time to first event of the composite of hospitalisation for heart failure or cardiovascular death. The secondary endpoints were a renal composite endpoint and all-cause mortality.

Major adverse cardiovascular events

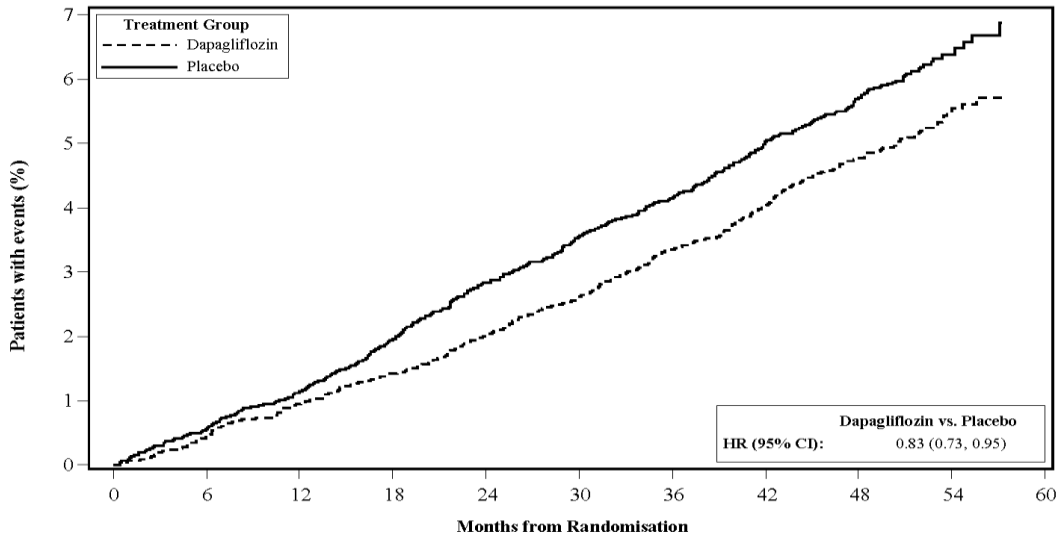
Dapagliflozin 10 mg demonstrated non-inferiority versus placebo for the composite of cardiovascular death, myocardial infarction or ischaemic stroke (one-sided $p < 0.001$).

Heart failure or cardiovascular death

Dapagliflozin 10 mg was superior to 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



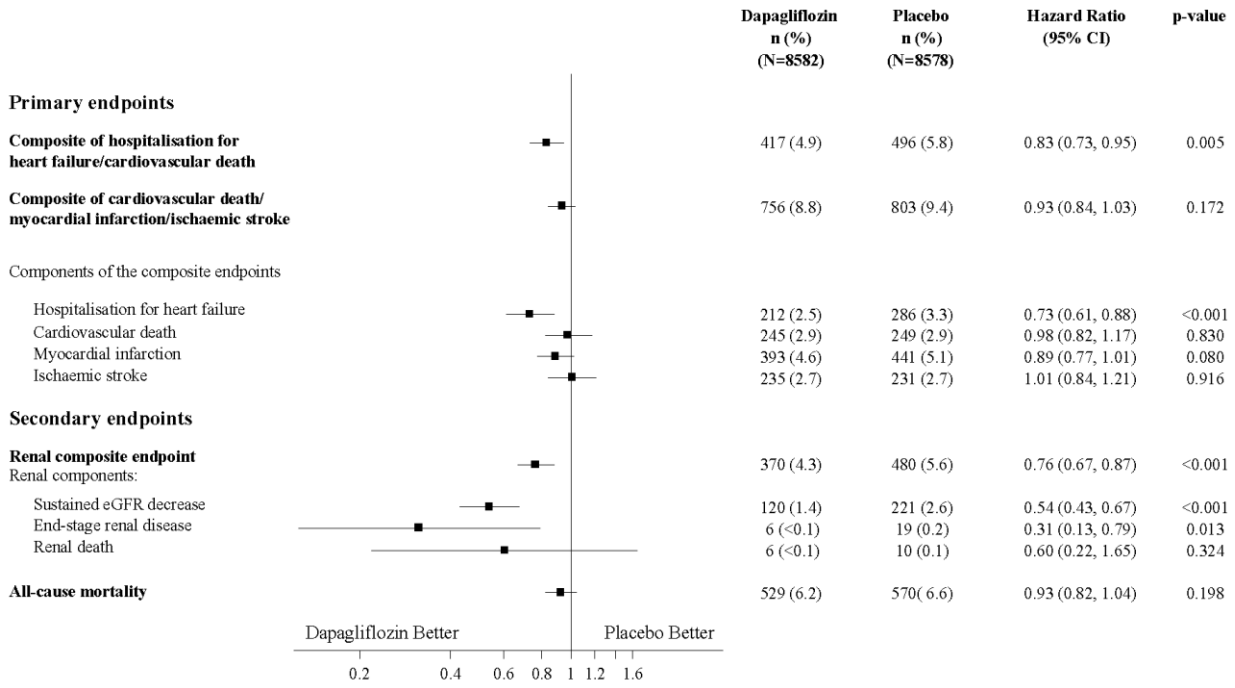
Patients at risk

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.

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

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 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 for single components. 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.

Nephropathy
Dapagliflozin reduced the incidence of events of the composite of confirmed sustained eGFR decrease, end-stage renal disease, renal or cardiovascular death. The difference between groups was driven by reductions in events of the renal components; sustained eGFR decrease, end-stage renal disease and renal death (Figure 2).

The hazard ratio for time to nephropathy was 0.53 (95% CI 0.43, 0.66) for dapagliflozin versus placebo.

In addition, dapagliflozin reduced the new onset of sustained albuminuria (hazard ratio 0.79 [95% CI 0.72, 0.87]) and led to greater regression of macroalbuminuria (hazard ratio 1.82 [95% CI 1.51, 2.20]) compared with placebo

העדכון המהותי בעלון לצרכן הוא:

2. לפני שימוש בתרופה

אזהרות מיוחדות הנוגעות לשימוש בפורסיגה

פנה לרופא באופן מיידי אם הנך מפתח שילוב של התסמינים הבאים: כאב,רגישות, אודם או נפיחות באזור איברי המין או באיזור בין איברי המין ופי הטבעת, בלווי חום או תחושה כללית רעה. תסמינים אלה עלולים להוות סימן לזיהום נדיר אך חמור ואף מסכן חיים, הנקרא **Fournier's gangrene/necrotising fasciitis of the perineum)**, הזיהום משמיד את הרקמה תחת העור וחייב להיות מטופל באופן מיידי

לפני הטיפול בפורסיגה ספר לרופא, לרוקח או לאחות אם:

- הנך סובל מבעיה בתפקודי הכבד -~~ייתכן והרופא ינחה אותך להתחיל במינון נמוך יותר של התרופה.~~
- ~~יש לך הסטוריה של מחלת לב חמורה או אם היה לך שבץ מוחי.~~

- הנך מקבל טיפול תרופתי נגד יתר לחץ דם, ויש לך הסטוריה של לחץ דם נמוך. מידע נוסף למטה בסעיף "אם אתה לוקח, או אם לקחת לאחרונה, תרופות אחרות [...]".
- הנך סובל מרמות גבוהות מאד של גלוקוז בדם, אשר עלולות להביא להתייבשות (איבוד של נוזלים רבים מדי בגוף). סימנים אפשריים של התייבשות מפורטים בתחילת סעיף 4 "תופעות לוואי". לפני התחלת הטיפול בפורסיגה, אנא תידע את הרופא שלך אם יש לך סימן מסימנים אלו.
- הנך סובל או פיתחת בחילה, הקאה, או חום, או אינך מסוגל לאכול או לשתות. תנאים אלו יכולים להביא להתייבשות. הרופא עשוי להנחות אותך להפסיק ליטול פורסיגה עד להחלמה, כדי למנוע התייבשות.
- ~~הנך סובל מזיהומים בדרכי השתן לעיתים קרובות, בעת השימוש בתרופה קיים סיכון מוגבר לזיהום בדרכי השתן (יתכן והרופא יפסיק זמנית את הטיפול בתרופה עם הופעת זיהום חריף בדרכי השתן)~~
- ~~אין להתחיל טיפול בפורסיגה אם הנך מעל גיל 75.~~
- ~~אין להתחיל טיפול בפורסיגה אם הנך נוטל תרופה אחרת לטיפול בסוכרת המכילה פיוגליטזון (Pioglitazone).~~
- ~~יש לך עלייה במספר תאי דם אדומים בדם הנראית בבדיקות.~~

4. <u>תופעות לוואי</u>

כמו לכל תרופה, השימוש בפורסיגה עלול לגרום לתופעות לוואי בחלק מהמשתמשים. אל תיבהל למקרא רשימת תופעות הלוואי. ייתכן ולא תסבול מאף אחת מהן.

פנה מיידית לרופא או לבית החולים הקרוב, במידה ואתה מבחין באחת מתופעות הלוואי שלהלן:

- אנגיואדמה, תופעת לוואי נדירה מאד (עלולה להשפיע על עד 1 מתוך 10,000 מטופלים).

סימנים של אנגיואדמה:
- נפיחות בפנים, בלשון או בגרון
- קשיי בליעה
- סרפדת וקשיי נשימה

- **זיהומים באזור הגניטלי (Fournier's gangrene/necrotising fasciitis of the perineum),**

זיהום חמור ברקמות הרכות באברי המין או באזור בין איבר המין ופי הטבעת, תופעה נדירה מאד.

תופעות לוואי אחרות בעת שימוש בפורסיגה:

תופעות לוואי שמופיעות לעיתים קרובות (משפיעות על עד 1 מתוך 10 מטופלים):
- זיהום גניטלי (פטרייתי) בנרתיק או בפין (הסימנים יכולים לכלול גרוי, גרוד, הפרשות לא רגילות או ריח לא רגיל)
- כאב גב
- מתן שתן רב יותר מהרגיל או מתן שתן לעיתים קרובות יותר
- שינוי ברמת הכולסטרול או השומנים בדם (נראה בבדיקות)
- שינוי בכמות תאי הדם האדומים בדם (נראה בבדיקות)
- שינוי ברמות הפינוי הקראטנין הכלייתי (נראה בבדיקות) <u>בתחילת הטיפול</u>
- סחרחורת
- פריחה

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

- השתנה לילית
- יובש בפה
- ירידה במשקל
- עליה בקראטינין (נצפה בבדיקות דם) בתחילת הטיפול
- עליה ברמות אוריאה (נצפה בבדיקות דם) ~~שינויים בבדיקות דם (לדוגמא קראטינין או אוריאה)~~
- ~~ירידה בפעילות הכליה~~

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

רוקחת ממונה
אסטרהזניקה (ישראל) בע"מ

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