Zorginstituut Nederland

> Return address PO Box 320, 1110 AH Diemen

To the Minister of Health, Welfare and Sport
PO Box 20350
2500 EJ THE HAGUE

2023013146

National Health Care Institute
Care
Medicinal Products

Willem Dudokhof 1
1112 ZA Diemen
PO Box 320
1110 AH Diemen
www.zorginstituutnederland.nl
info@zinl.nl

T +31 (0)20 797 85 55

Contact
warcg@zinl.nl

Date 23 May 2023
Re: Expansion of further condition for dapagliflozin (Forxiga®)

Our reference
2023013146

Dear Mr Kuipers,

In your letter of 3 April 2023 (CIBG-23-05284), you asked the National Health Care Institute to advise you on the expansion of the List 2 condition for dapagliflozin (Forxiga®).

The National Health Care Institute has now completed the substantive assessment. The considerations are set out in the annex.

Background
Dapagliflozin has been included in the Medicine Reimbursement System (GVS) on List 1A in cluster 0A10BXAO V along with canagliflozin, empagliflozin and ertugliflozin. The reimbursement is arranged through List 2 conditions:

Only for insured persons:
1. *with type 2 diabetes mellitus who cannot be treated with the combination of metformin and a sulfonylurea derivative, who do not use insulin and use this medicinal product as a dual or triple treatment in combination with metformin and/or a sulphonylurea derivative,*
2. *aged eighteen and older with symptomatic (NYHA II-IV) chronic heart failure with reduced ejection fraction (LVEF<40%),*
3. *18 years and older with type 2 diabetes mellitus with a very high risk of cardiovascular disease, or*
4. *aged eighteen or older with chronic kidney disease.*

Current request
The current request relates to the expansion of the reimbursement condition for symptomatic (NYHA II-IV) chronic heart failure, and is based on the registration granted by the European Medicines Agency (EMA) in 2023 for the treatment of adults with symptomatic chronic heart failure regardless of the ejection fraction (LVEF). The now requested expansion is therefore specifically related to patients with symptomatic (NYHA II-IV) chronic heart failure and an LVEF >40%. The recommended dosage in that case is 10 mg per day, added to the standard background treatment for heart failure.

Substantive assessment
Pharmacotherapy

National Health Care Institute
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The National Health Care Institute concluded that dapagliflozin meets the established medical science and medical practice for patients with symptomatic (NYHA II-IV) chronic heart failure with LVEF >40%. Dapagliflozin has an equal value compared to empagliflozin.

Budget impact analysis
The expansion of the List 2 condition of dapagliflozin is expected to be accompanied by very limited additional costs for the pharmaceutical budget, due to a small difference in price between dapagliflozin and empagliflozin. The National Health Care Institute has therefore not developed a budget impact analysis.

Advice from the National Health Care Institute
Dapagliflozin is already included on List 1A of the GVS (cluster 0A10BXAO V) with further conditions. On the above grounds, the National Health Care Institute recommends that you adjust the current List 2 condition (for symptomatic *(NYHA II-IV) chronic heart failure with reduced ejection fraction (LVEF <40%*) as follows:

Condition:
For an insured person aged eighteen years or older with symptomatic (NYHA II-IV) chronic heart failure.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

Annex 1: Substantive assessment

Annex 1

National Health Care Institute
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Assessment of therapeutic value

1.1 Background

Heart failure is defined as a failure of the heart to pump, resulting in a complex of signs and symptoms. Diagnosis should be based on symptoms, examination findings and objective evidence of structural or functional abnormality of the resting heart. The cause may be related to heart muscle loss or weakness (often due to a history of myocardial infarction), but may also be related to prolonged pressure or volume overload. Heart failure is a chronic progressive disease. Patients may remain stable for a period of time with adequate therapy, but the damage and dysfunction of the heart muscle increase over time. Ultimately, this leads to a phase of deteriorating heart failure where the patient experiences episodes of decompensation despite adequate therapy. After each episode, the cardiac function continues to deteriorate and the risk of hospitalisation or death increases [1, 2].

With the help of ultrasound, 3 types of heart failure can be distinguished [1]:
1. Heart failure with maintained LVEF of >50% (HFpEF);
2. Heart failure with moderate LVEF of 40-49% (HFmrEF);
3. And heart failure with decreased LVEF of <40% (HFrEF)

In systolic dysfunction (HFrEF and HFmrEF), there is insufficient contraction of the heart during systole, for example due to a myocardial infarction. Diastolic dysfunction (HFpEF) does not involve reduced contraction but rather a stiffening of the heart muscle. A known cause of this is long-term hypertension. On average, patients with HFmrEF, like patients with HFrEF, are younger and more frequently male. Compared to patients with HFpEF, they more often have a history of coronary artery disease. However, ambulatory patients with HFmrEF have lower mortality than patients with HFrEF; comparable to HFpEF. Patients with HFpEF are generally more likely to be female, on average older, and suffer more frequently from atrial fibrillation, chronic renal disease and other non-cardiovascular comorbidities compared to patients with HFrEF [1, 2].

Chronic heart failure is characterised by symptoms of shortness of breath or fatigue, at rest or during exercise. Usually there are also signs of fluid retention such as pulmonary oedema, peripheral oedema, ascites and/or weight gain. In more severe cases, tachycardia and tachypnoea may occur [1].

The most commonly used classification for heart failure severity is the New York Heart Association (NYHA) classification.
This is the guiding principle of the Dutch guideline. It defines four classes based on the severity of the symptoms during exercise. This classification is a snapshot and may vary over time. A higher NYHA class is accompanied by a reduced quality of life [1, 2].

The mean five-year mortality after diagnosis is approximately 35%. The one-year mortality of patients at heart failure outpatient clinics is approximately 6% for HFpEF and 9% for HFrEF [1].

1.2 Guidelines

Based on the guidelines of the Dutch College of General Practitioners (NHG, 2021) and the *European Society of Cardiology* (ESC), it can be concluded that the standard treatment for both HFmrEF and HFpEF patients usually consists of an angiotensin-converting enzyme (ACE)
inhibitor, angiotensin II receptor blocker (ARB) or angiotensin receptor neprilysin inhibitor (ARNi), possibly a diuretic, beta blocker and/or mineral corticoid receptor antagonist (MRA). However, evidence for these treatments in patients with LVEF>40% on firm outcome parameters is very limited. As yet, no recommendation has been made for the use of an SGLT2 inhibitor [1, 2].

The latest AHA/ACC/HFSA (*American Heart Association, American College of Cardiology, Heart Failure Society of America*) guideline for the treatment of heart failure (2022) recommends empagliflozin for HFmrEF and HFpEF.

It is mentioned that empagliflozin may have added value in reducing hospitalisations for heart failure and cardiovascular mortality. The quality of the evidence for this recommendation is considered moderate (Class 2A). As yet, no recommendation has been made for dapagliflozin [3].

According to the SmPC, dapagliflozin can be added to the standard treatment [4]. This can consist of different combinations of heart failure medication. Dapagliflozin has the same place in the treatment algorithm as empagliflozin. Empagliflozin was assessed by the National Health Care Institute in January 2023 for this indication and is now being reimbursed for this indication [5].

1.3 Desirable effects

1.3.1 Dapagliflozin

The effect of dapagliflozin in patients with symptomatic chronic heart failure (NYHA II-IV) and LVEF >40% was investigated in one randomised, double-blind, placebo-controlled multicentre phase III study (DELIVER) [6]. In this study, 3126 patients were treated with dapagliflozin 10 mg and 3127 patients were treated with a placebo, with a median treatment duration of 27.6 months. The average age of the study population was 72 years, and 56% was male. At baseline, 75% of patients were classified as NYHA class II, 24% as class III and 0.3% as class IV. The median LVEF was 54; 34% of 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 (DM2). The baseline treatment included ACEi/ARB/ARNi (77%), beta-blockers (83%), diuretics (98%) and MRA (43%). The mean eGFR was 61 ml/min/1.73 m^2 at baseline [6].

Table 1 shows the key results for the critical outcome parameters.

Outcome parameter	Number of patients with an event		HR (95% CI)
	Dapagliflozin N=3131	Placebo N=3132	
Primary: Composition of an urgent consultation for HF, hospitalisation	512 (16.4%)	610 (19.5%)	0.82 (0.73-0.92)

for HF or CV mortality			
Hospitalisation for HF	329 (10.5%)	418 (13.3%)	0.77 (0.67-0.89)
Urgent consultation for HF	60 (1.9%)	78 (2.5%)	0.76 (0.55-1.07)
CV mortality	231 (7.4%)	261 (8.3%)	0.88 (0.74-1.05)
Overall mortality	497 (15.9%)	526 (16.8%)	0.94 (0.83-1.07)

Table 1: Main results of the DELIVER study [6]. CI: Confidence Interval, CV: Cardiovascular, HF: Heart Failure, HR: Hazard Ratio.

The quality of life of patients in the DELIVER study was measured by the *Kansas City Cardiomyopathy Questionnaire* (KCCQ) *clinical symptom score (CSS).* At 8 months, 51% of patients in the dapagliflozin group showed ≥5 points improvement in the KCCQ-CSS compared to 47% in the placebo group. In the dapagliflozin group, 21% of patients had a ≥5 point deterioration in the KCCQ-CSS compared to 26% in the placebo group [7].

1.3.2 Empagliflozin

The effect of empagliflozin in patients with symptomatic chronic heart failure (NYHA II-IV) and LVEF >40% was investigated in one randomised, double-blind, placebo-controlled multicentre phase III study (EMPEROR-Preserved) [8]. In this study, 2997 patients were treated with empagliflozin 10 mg and 2991 patients were treated with a placebo, with a median treatment duration of 26.2 months. The study population consisted of 55.3% males and 44.7% females with a mean age of 71.9 years (range: 22-100 years); 43.0% were 75 years or older. Of the study population, 75.9% was white, 13.8% was Asian and 4.3% was black/African-American. At randomisation, 81.5% of patients was classified as NYHA class II, 18.1% as class III and 0.3% as class IV. The population of the EMPEROR-Preserved study included patients with LVEF <50% (33.1%), patients with LVEF 50 to <60% (34.4%), and patients with LVEF ≥60% (32.5%). The baseline treatments included ACEi/ARB/ ARNi (80.7%), beta-blockers (86.3%), MRA (37.5%) and diuretics (86.2%). The mean eGFR at baseline was 60.6 ml/min/1.73 m^2. 49% of the included patients had DM2 [8].

Table 2 shows the key results for the critical outcome parameters.

Outcome parameter	Number of patients with an event		HR (95% CI)
	Empagliflozin N=2997	Placebo N=2991	
Primary: Composition of hospitalisation for HF or CV mortality	415 (13.8%)	511 (17.1%)	0.79 (0.69-0.90)
Hospitalisation for HF	259 (8.6%)	352 (11.8%)	0.71 (0.60-0.83)
CV mortality	219 (7.3%)	244 (8.2%)	0.91 (0.76-1.09)
Overall mortality	422 (14.1%)	427 (14.3%)	1.00 (0.87-1.15)

Table 2: Main results of the EMPEROR-Preserved study [8]. CI: Confidence Interval, , CV: Cardiovascular, HF: Heart Failure, HR: Hazard Ratio*.*

The quality of life of patients in the EMPEROR-Preserved study was also measured with the KCCQ-CSS. At 8 months, 37.6% of patients in the empagliflozin group showed ≥5 points improvement in the KCCQ-CSS compared to 34.6% in the placebo group. At 8 months, 27.4% of patients in the empagliflozin group showed ≥5 points deterioration in the KCCQ-CSS compared to 30.3% in the placebo group [9].

1.3.3 Indirect comparison

A direct comparative study between dapagliflozin and empagliflozin has not been conducted. However, the DELIVER and EMPEROR-Preserved phase III studies are largely similar in design and implementation. There are small differences in the number of patients included, duration of follow-up, and inclusion and exclusion criteria. This is not expected to have a significant impact on the results. When the results of both studies are compared indirectly, the results appear consistent. Both SGLT2 inhibitors are likely to have a clinically relevant effect on the prevention of hospitalisations for heart failure. The National Health Care Institute considers this a critical outcome parameter. In addition, neither dapagliflozin nor empagliflozin is likely to have a clinically relevant effect on cardiovascular or overall mortality. The effects on the quality of life also seem similar for both medicinal products.

In 2022, Vaduganathan et al. performed a meta-analysis that included both the DELIVER and EMPEROR-Preserved studies [10]. This meta-analysis also shows that the results of both SGLT2 inhibitors are consistent. Pooling the results of both studies will result in a clinically relevant effect on the prevention of heart failure hospitalisations for both (HR 0.74 (95% CI: 0.67-0.83). In addition, a statistically almost significant effect is found on the risk of cardiovascular death (HR 0.88; 95% CI: 0.77-1.00).

No statistically significant effect on overall mortality is observed (HR 0.97 (95% CI: 0.88-1.06). The meta-analysis also shows that the effectiveness of both SGLT2 inhibitors is similar in different subgroups (regardless of LVEF, age, gender, race, NYHA class, etc.) [10].

1.4 Undesirable effects

The most common and severe side effects in the SmPCs of dapagliflozin and empagliflozin are described below [11, 4]. Their side effects profiles are similar.

	System/organ class	**Dapagliflozin [4]**	**Empagliflozin [11]**
Very common	Nutritional and metabolic disorders	Hypoglycaemia (when used with a sulphonylurea derivative or insulin)	Hypoglycaemia (when used with a sulphonylurea derivative or insulin)
Common	Infections and parasitic diseases	Vulvovaginitis, balanitis and related genital	Vaginal candidiasis,

		infections, Urinary tract infection	vulvovaginitis, balanitis and other genital infections, urinary tract infection (including pyelonephritis and urosepsis)
	Nutritional and metabolic disorders		Thirst
	Gastrointestinal disorders		Constipation
	Nervous system disorders	Dizziness	
	Skin and subcutaneous tissue disorders	Rash	Itching, rash
	Blood vessel disorders	Volume depletion	
	Musculoskeletal and connective tissue disorders	Back pain	
	Kidney and urinary tract disorders	Dysuria Polyuria	Urinating more often
	Testing	Increased haematocrit, decreased renal clearance creatinine during initial treatment, dyslipidaemia	Serum lipids increased
Severe		Genital infection, Fournier gangrene, hypoglycaemia, volume depletion, urinary tract infections	Genital infection, Fournier gangrene, hypoglycaemia, volume depletion, urinary tract infections

In the DELIVER study, 1361 patients (43.5%) in the dapagliflozin group and 1423 patients (45.5%) in the placebo group experienced severe adverse effects [12, 6]. In the EMPEROR-Preserved study, these were 1436 patients (47.9%) in the empagliflozin group and 1543 (51.6%) in the placebo group [8, 13]. Furthermore, during the DELIVERY study, 182 patients (5.8%) in the dapagliflozin group and 181 (5.8%) in the placebo group discontinued due to an adverse effect [12, 6]. In the EMPEROR-Preserved study, these were 571 patients (19.1%) in the

empagliflozin group and 551 patients (18.4%) in the placebo group [8, 13]. Thus, there do not appear to be any relevant differences between the two SGLT2 inhibitors in terms of adverse effects and the number of patients who discontinue treatment.

1.5 Budget impact analysis

As previously mentioned, dapagliflozin is currently listed in the GVS on List 1A in a cluster with canagliflozin, empagliflozin and ertugliflozin. Empagliflozin is already reimbursed for the indication for which reimbursement is now requested for dapagliflozin. It is expected that in the future there will be a major shift in patients. It is not expected that many patients who are not currently being treated with empagliflozin will be treated with dapagliflozin. As the price of both medicinal products is similar (€1.49 per tablet dapagliflozin versus €1.41 per tablet empagliflozin [14, 15]), this is therefore unlikely to lead to high additional costs. For this reason, no budget impact analysis has been done.

1.6 Conclusion

The National Health Care Institute concludes that dapagliflozin meets the established medical science and medical practice for patients with symptomatic (NYHA II-IV) chronic heart failure with LVEF >40%. Dapagliflozin has an equal value compared to empagliflozin.

1.7 Pharmacotherapeutic Kompas advice

The new advice is in line with the advice for empagliflozin and reads as follows:

In symptomatic chronic heart failure with moderate or sustained ejection fraction (LVEF > 40%), dapagliflozin is recommended for patients with NYHA classes II to IV. Dapagliflozin appears to reduce the number of hospitalisations for heart failure, but in general has no effect on mortality or quality of life.

1.8 Literature

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