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Date 7 December 2023
Re: Letter report expansion indication empagliflozin (Jardiance®)

Our reference
2023029826

Dear Mr Kuipers,

In your letter of 25 September 2023 (CIBG-23-06082), you asked the National Health Care Institute to advise you on the expansion of the List 2 condition for empagliflozin (Jardiance®). The National Health Care Institute has completed the substantive assessment. The considerations are set out in the annex.

Background

Empagliflozin is an oral blood glucose reducing agent that selectively inhibits the sodium/glucose co-transporter 2 (SGLT2) in the renal tubules. Empagliflozin has been included in the Medicine Reimbursement System (GVS) as part of List 1A in cluster 0A10BXAO V along with canagliflozin, dapagliflozin and ertugliflozin. The reimbursement of empagliflozin is based on List 2 conditions.

Current assessment

The current assessment is aimed at the expansion of the List 2 conditions of empagliflozin, for adults with chronic kidney disease (CKD).
Dapagliflozin is the comparative treatment against which empagliflozin is tested. Dapagliflozin has previously been evaluated by the National Health Care Institute for the same indication and is now also being reimbursed.

Substantive assessment

Pharmacotherapy
Empagliflozin complies with established medical science and medical practice for the treatment of CKD. Based on the available evidence in Annex 1, empagliflozin is equivalent to dapagliflozin for CKD.

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

Advice from the National Health Care Institute

Empagliflozin is already included on List 1A of the GVS (cluster 0A10BXAO V) with further conditions. For the above reasons, the National Health Care Institute advises you to extend the current List 2 condition as follows:

Condition: For an insured person aged eighteen or older with chronic kidney disease.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

Annex 1: Substantive assessment

National Health Care Institute

Date
7 December 2023

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Annex 1

National Health Care Institute

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1.1 List of abbreviations

ACE inhibitor	Angiotensine Converting Enzyme inhibitor
ACR	Albumin-Creatinine Ratio
ARB	Angiotensin receptor blocker
CKD	Chronic kidney disease
CV	Cardiovascular
DM2	Type 2 diabetes mellitus
eGFR	estimated Glomerular Filtration Rate
ESRF	End-stage renal failure
FMS	Federation of Medical Specialists
GVS	Medicine Reimbursement System
HF	Heart failure
IDMC	Independent Data Monitoring Committee
KDIGO	Kidney Disease: Improving Global Outcomes
NHG	Dutch College of General Practitioners
NNT	Number Needed to Treat
SGLT2	Sodium-glucose co-transporter 2

1.2 Background

Chronic kidney disease (CKD) is diagnosed when, during at least 3 months, the patient has:

- Impaired kidney function (eGFR<60 ml/min/1.73m2) and/or
- Increased albuminuria and/or
- Specific sediment abnormalities[1].

CKD is staged based on kidney function and the extent of albuminuria. There are 6 stages of kidney function, and 3 stages of albuminuria; see figure 1. Patients generally receive primary healthcare unless there is severe increased albuminuria (stage A3).[1]

Patients with CKD are at increased risk of cardiovascular disease and end-stage renal failure. Based on the established stages of CKD, a risk stratification is created for the risk of cardiovascular damage, progression of kidney disease and mortality, respectively; see figure 1.[1]

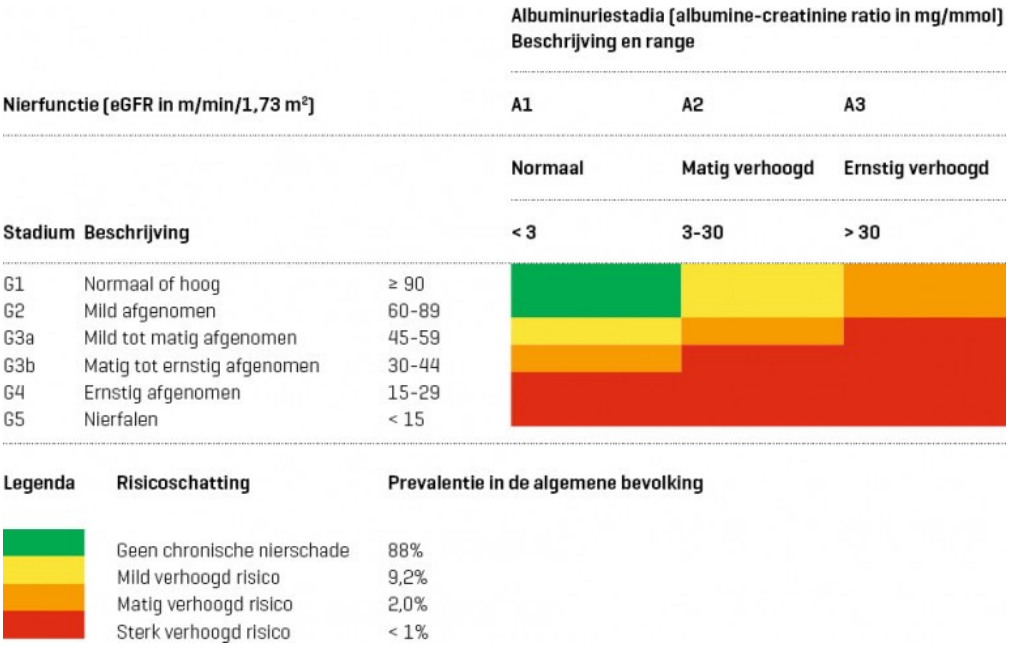

Fig. 1: CKD stages and associated categorisation of the risk of cardiovascular damage, progression of kidney disease and mortality. On the left are the stages of kidney disease, from G1 to G5. On the right are the albuminuria stages (A1 to A3), and the risk estimates associated with the combined stages of kidney disease and albuminuria.[1]

[1] Urinal sediment abnormalities such as dysmorphic erythrocytes and/or cell cylinders.

1.3 Guidelines

The treatment of CKD is described in the Standard on Chronic Kidney Disease (Chronische Nierschade, 2018) of the Dutch College of General Practitioners (NHG) and in the multidisciplinary guideline on chronic kidney disease (Chronische Nierschade, 2018) of the Federation of Medical Specialists (FMS).[2, 1] In addition, the international network of nephrologists 'KDIGO' (Kidney Disease: Improving Global Outcomes) has published a treatment guideline for blood pressure management in patients with CKD (2021). [3] The KDIGO is also developing a treatment guideline for the diagnosis and treatment of CKD. This guideline is expected to be completed by the end of 2023. A published draft version is available for commentary[2].[4]

In all patients with CKD, life style advice is recommended, including efforts to maintain a healthy weight, adequate exercise, quitting smoking and limiting salt intake to a maximum of 6 grams per day. Medical management consists of cardiovascular risk management with statins (possibly in combination with ezetimibe) and blood pressure lowering agents. The choice of a blood pressure lowering agent depends on kidney function, albuminuria and other comorbid disorders and conditions. In case of moderately or severely elevated albuminuria [albumin-creatinine ratio (ACR) ≥ 3 mg/mmol], an angiotensin converting enzyme inhibitor (ACE inhibitor) or an angiotensin receptor blocker (ARB) is preferred.[2, 1]

The NHG standard on chronic kidney disease and the FMS's multidisciplinary guideline on chronic kidney disease do not discuss the use of SGLT2 inhibitors for CKD. However, SGLT2 inhibitors are preferred in patients with type 2 diabetes mellitus (DM2) and CKD. According to the KDIGO treatment guideline for blood pressure management for CKD, SGLT2 inhibitors may be used more widely in the treatment of CKD, given their positive effect on cardiovascular events, kidney disease progression and survival. However, the guideline notes that acute deterioration of kidney function is observed when initiating treatment with SGLT2 inhibitors, as is also observed with ACE inhibitors and ARBs. It is up to the treating physician to assess with the patients whether this deterioration is acceptable. [3] In the revised draft guideline for the treatment of CKD, KDIGO recommends the use of SGLT2 inhibitors as maintenance treatment. This applies to patients with CKD and:

- DM2 with an eGFR ≥20 ml/min per 1.73 m2 or
- Heart failure or
- A high risk of kidney disease progression, characterised by an eGFR of ≥20 ml/min per 1.73 m2 with an ACR ≥200 mg/g.
- An eGFR of 20 to 45 ml/min/1.73 m2 with an ACR <200 mg/g. [4]

Empagliflozin is ranked in the same position as dapagliflozin in the treatment algorithm. The National Health Care Institute evaluated dapagliflozin for this indication in March 2022. It has since been reimbursed for this.[5]

[2] The draft version of the KDIGO guideline for CKD is a version available for *public review.* This was accessible to the National Health Care Institute at the time of this assessment.

1.4 Desirable effects

1.4.1 Empagliflozin

The effect of empagliflozin on CKD was investigated in the EMPA-KIDNEY study.[6] Subjects in this randomized, double-blind, placebo-controlled study were patients with CKD who had an eGFR of 20 - 45 ml/min/1.73m^2 or an eGFR of 45 - 90 ml/min/1.73m^2 with an ACR of at least 200 mg/g. In the study, 3304 patients were treated with empagliflozin 10 mg and 3305 patients were treated with placebo (median follow-up: 24.3 months). The primary outcome parameter was a composite measure of kidney disease progression and cardiovascular death. Kidney disease progression was defined in the study as:

- End-stage renal failure (ESRF), marked by the initiation of maintenance dialysis or kidney transplant.
- A sustained decrease in eGFR to less than 10 ml/min/1.73 m^2.
- A sustained decrease in eGFR of at least 40% compared to eGFR at the start of the study.
- Renal death.

An important secondary endpoint was the composite outcome parameter for 'hospitalisation due to heart failure', 'cardiovascular death', 'hospitalisation regardless of cause' and 'death regardless of cause'. The individual components of this endpoint are also included as tertiary endpoints.

The average age of the study population was 63.3 years, and 66.8% was male. At baseline, the mean eGFR was 37.3 ml/min/1.73 m2 and the median ACR was 329 mg/g. 44.4% of patients had DM2 and 26.7% had cardiovascular disease; 85.2% were taking an ACE inhibitor or ARB.

The study was terminated early in consultation with an Independent Data Monitoring Committee (IDMC) due to convincing results. The analyses were performed for 624 events, instead of the planned 1070 events at the primary endpoint (58% maturity). Table 1 shows the key results for the critical outcome parameters.

Table 1. EMPA-KIDNEY study results overview. CV=cardiovascular, HR=hazard ratio, CI=confidence interval, NNT=number needed to treat, HF=heart failure

Outcome parameter	Number of patients with an event		HR (95% CI)
	Empagliflozin N=3304	Placebo N=3305	
Primary: Composition of kidney disease progression and CV death	432 (13.1%)	558 (16.9%)	0.72 (0.64-0.82) NNT: 26
Deterioration of kidney function, renal failure or renal death	384 (11.6%)	504 (15.2%)	0.71 (0.62-0.81)
Death regardless of cause	148 (4.5%)	167 (5.1%)	0.87 (0.70-1.08)
Hospitalisation for HF or CV death	131 (4.0%)	152 (4.6%)	0.84 (0.67-1.07)

1.4.2 Dapagliflozin

The effect of dapagliflozin in CKD was studied in the DAPA-CKD study.[7] This is a randomized, double-blind, placebo-controlled, phase III study that investigated the effectiveness and safety of dapagliflozin, added to standard treatment in adult patients with CKD. In the study, 2152 patients were treated with dapagliflozin 10 mg and 2152 patients were treated with placebo (median follow-up duration: 2.4 years).

The average age of the study population was 61.8 years, and 66.9% was male. At baseline, the mean eGFR was 43.1 ml/min/1.73 m2 and the median ACR was 949.3 mg/g. 37.4% of patients had a CV disorder and 67.5% had DM2; 97.0% was taking an ACE inhibitor or ARB.

The primary endpoint of the DAPA-CKD study was a combination of a sustained eGFR decline of ≥50%, ESRF, and renal or cardiovascular death. A time-to-event analysis was applied. ESRF was defined as maintenance dialysis for ≥28 days, kidney transplantation or sustained eGFR < 15 ml/min/1.73m^2. Key secondary endpoints were:

- Sustained eGFR decrease of ≥50%, ESRF or renal death (composite)
- Hospitalization due to heart failure or death due to cardiovascular cause (composite)
- All-cause mortality

The study was terminated early in consultation with an IDMC due to convincing results. The analyses were performed for 509 events, instead of the planned 681 events at the primary endpoint (75% maturity). Table 2 shows the key results for the critical outcome parameters.

Table 2. Outcomes DAPA-CKD study.

Outcome parameter	Number of patients with an event		HR (95% CI)
	Dapagliflozin N=2152	Placebo N=2152	
Primary: Composition of kidney disease progression and death due to CV or renal causes	197 (9.2%)	213 (14.5%)	0.61 (0.51-0.72) NNT: 19
Deterioration of kidney function, renal failure or renal death	142 (6.6%)	243 (11.3%)	0.56 (0.45-0.68)
Death regardless of cause	101 (4.7%)	146 (6.8%)	0.69 (0.53-0.88)
Hospitalisation for HF or CV death	100 (4.6%)	138 (6.4%)	0.71 (0.55-0.88)

1.4.3 Indirect comparison empagliflozin and dapagliflozin

No direct comparative effectiveness and safety study of empagliflozin and dapagliflozin for CKD has been performed. When the results of the studies described above are compared indirectly, the results appear to consistently indicate the same direction for the different outcome parameters. However, the effect of empagliflozin in the EMPA-KIDNEY study appears to be less explicit than the effect of dapagliflozin in the DAPA-CKD study. This can be explained, for example, by differences in the number of included patients (6609 vs. 4304), duration of follow-up (2.0 vs. 2.4 years), maturity of the data (58% vs. 75%) and the definition of the different outcome parameters. In the EMPA-KIDNEY study, due in particular to differences in selection criteria, patients were likely to have a lower background risk of having a renal/cardiovascular event or death compared to patients in the DAPA-CKD study. In the EMPA-KIDNEY study, all patients with DM2 and atherosclerotic cardiovascular disease (myocardial infarction, angina, stroke or peripheral arterial disease) were excluded. In the DAPA-CKD study, this was not the case. In addition, the EMPA-KIDNEY study included patients without albuminuria (20.1% of included patients), as opposed to the DAPA-CKD study where all patients had to have an ACR >200 mg/g. There is also a large difference in the number of enrolled patients with DM2 (44.4% vs. 67.5%). [6, 7]

The recently published *Nuffield Department of Population Health Renal Studies Group* meta-analysis *(2022)* examines the effects of SGLT2 inhibitors on different outcome parameters in patients with CKD with/without DM2. The meta-analysis included the EMPA-KIDNEY and DAPA-CKD studies. This shows that the effect of dapagliflozin and empagliflozin on kidney disease progression is similar, regardless of diabetes status.[8] The KDIGO Concept Guideline also does not distinguish between the two SGLT2 inhibitors. [4]

Based on the above analysis, the National Health Care Institute considers it likely that there are no clinically relevant differences between the desirable effects of empagliflozin and dapagliflozin in patients with CKD.

1.5 Undesirable effects

The most common and severe side effects in the SmPCs for empagliflozin and dapagliflozin are described below.[9, 10] The side effects profiles are similar.

	System/organ class	Empagliflozin [9]	Dapagliflozin [10]
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 disorders	Vaginal candidiasis, vulvovaginitis, balanitis and other genital infections, urinary tract infection (including pyelonephritis and urosepsis)	Vulvovaginitis, balanitis and related genital infections, Urinary tract infection
	Nutritional and metabolic disorders	Thirst	
	Gastrointestinal disorders	Constipation	
	Nervous system disorders		Dizziness
	Skin and subcutaneous tissue disorders	Itching, rash	Rash
	Blood vessel disorders		Volume depletion
	Musculoskeletal and connective tissue disorders		Back pain
	Kidney and urinary tract disorders	Urinating more often	Dysuria Polyuria
	Testing	Serum lipids increased	Increased haematocrit, decreased renal clearance creatinine during initial treatment, dyslipidaemia
Severe		Genital infection, Fournier gangrene, hypoglycaemia, volume depletion, urinary tract infections	Genital infection, Fournier gangrene, hypoglycaemia, volume depletion, urinary tract infections

In the EMPA-KIDNEY study, 1167 patients (35.3%) in the empagliflozin group and 1088 patients (32.9%) in the placebo group experienced severe adverse events.[11] In the DAPA-CKD study, these were 633 patients (29.5%) in the

dapagliflozin group and 729 (33.9%) in the placebo group. [7] Furthermore, during the EMPA-KIDNEY study, 241 patients (7.3%) in the empagliflozin group and 232 (7.0%) in the placebo group discontinued treatment due to an adverse effect.[11] In the DAPA-CKD study, these were 118 patients (5.5%) in the dapagliflozin group and 123 patients (5.7%) in the placebo group.[7] Therefore, there do not appear to be any relevant differences between the two SGLT2 inhibitors in terms of adverse effects and number of discontinuations.

1.6 Budget impact analysis

As previously mentioned, empagliflozin is currently listed in the GVS on List 1A in a cluster with canagliflozin, dapagliflozin and ertugliflozin. Dapagliflozin is already reimbursed for the indication for which reimbursement is now requested for empagliflozin. It is expected that in the future there will be a shift in patients. It is not expected that many patients who are not currently being treated with dapagliflozin will be treated with empagliflozin. As the price of both medicinal products is similar (€1.41 per tablet empagliflozin versus €1.49 per tablet dapagliflozin), this is therefore unlikely to lead to (high) additional costs. [12, 13] A budget impact analysis has therefore not been conducted.

1.7 Conclusion

The National Health Care Institute concludes that empagliflozin meets the established medical science and medical practice for patients with CKD. In this respect, empagliflozin has an equal value compared to dapagliflozin.

1.8 Pharmacotherapeutic Kompas advice

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

Adding empagliflozin to the treatment of chronic kidney disease can be considered. This medicine inhibits the deterioration of kidney function and reduces the risk of cardiovascular death.

1.9 References

1. De Grauw W. DLK, Schenk P., et al. Chronische nierschade. NHG 2018.
2. Federatie Medisch Specialisten NIVN (2018). Chronische nierschade (CNS). Retrieved 15 August 2023, 2023, from https://richtlijnendatabase.nl/richtlijn/chronische_nierschade_cns/startpagina_-_chronische_nierschade_cns.html.
3. KDIGO. Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Practice Guideline 2021; 99: S1-S87.
4. KDIGO (2023). KDIGO 2023 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, Public Review Draft. Retrieved 15 August 2023, 2023, from https://kdigo.org/guidelines/ckd-evaluation-and-management/.
5. Nederland Z (2022). Farmacotherapeutisch rapport dapagliflozine (Forxiga®) bij de behandeling van chronische nierschade. Retrieved 18 September, 2023, from https://www.zorginstituutnederland.nl/publicaties/adviezen/2022/03/28/gvs-advies-dapagliflozine-forxiga-bij-chronische-nierschade.
6. The E-KCG, Herrington WG, Staplin N, et al. Empagliflozin in Patients with Chronic Kidney Disease. N Engl J Med 2023; 388: 117-27.
7. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med 2020; 383: 1436-46.
8. Nuffield Department of Population Health Renal Studies G and Consortium SiM-AC-RT. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet 2022; 400: 1788-801.
9. EMA (2023). SmPC empagliflozin Retrieved 3 November 2023, from https://www.ema.europa.eu/en/medicines/human/EPAR/jardiance#assessment-history-section.
10. EMA (2023, 18 May 2023). SmPC dapagliflozin. from https://www.ema.europa.eu/en/medicines/human/EPAR/forxiga.
11. EMA (2023). EPAR empagliflozin. Retrieved 4 November 2023, from https://www.ema.europa.eu/en/medicines/human/EPAR/jardiance#assessment-history-section.
12. Nederland Z (2023). Medicijnkosten empagliflozin. Retrieved 4 November 2023, from https://www.medicijnkosten.nl/zoeken?trefwoord=empagliflozine.
13. Nederland Z (2023). Medicijnkosten dapagliflozin. Retrieved 4 November 2023, from https://www.medicijnkosten.nl/zoeken?trefwoord=dapagliflozine.