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2024016031

Date 2 August 2024
Subject Extension of further conditions for empagliflozin (Jardiance®)

Our reference
2024016031

Dear Ms Agema,

The physicians' association in the Netherlands has submitted a request for expansion of the List 2 conditions for empagliflozin (Jardiance®). The National Health Care Institute has completed the assessment. The considerations involved are set out in this advisory letter.

Background
Empagliflozin is an oral blood glucose-lowering agent that selectively inhibits the sodium-glucose cotransporter 2 (SGLT2) in the renal tubuli. Empagliflozin has already been included in the Medicine Reimbursement System (GVS) on List 1A in cluster 0A10BXAO V along with canagliflozin, dapagliflozin and ertugliflozin. Reimbursement of empagliflozin is based on List 2 conditions. Those List 2 conditions are:

1. *For patients with type 2 diabetes mellitus who cannot be treated with a combination of metformin and a sulfonylurea derivative and who do not use insulin. In addition, empagliflozin must be used in combination with metformin or in combination with metformin and a sulfonylurea derivative.*
2. *For adults with symptomatic (NYHA II-IV) chronic heart failure.*
3. *For adults with an extremely high risk of cardiovascular disease (previously proven cardiovascular disease).*
4. *For adults with chronic kidney damage.*

Current assessment
This assessment is about extending the List 2 conditions for empagliflozin to include patients with glycogen storage diseases **type Ib** (GSD-Ib; Von Gierke disease) and **type XI** (GSD-XI; Fanconi-Bickel syndrome). Empagliflozin is not licensed (off-label) for these extremely rare indications. In collaboration with the patients' association VKS (*Adults, Children and Metabolic Diseases*), the professional group is therefore now asking for reimbursement for these rare indications. [The physicians' association comprises the Expertise Centre of the University Medical Centre in Groningen (UMCG), the platform Medicijn voor de Maatschappij (*Medicine for Society*), the Metabolic Diseases Section of the Dutch

Association for Pediatric Medicine, and INVEST (*Internists for Adults with a Hereditary Metabolic Disease*)]. The marketing authorisation holder for empagliflozin (Jardiance®) is backing that request.

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Substantive assessment
Pharmacotherapy
Based on the evidence in the pharmacotherapeutic assessment contained in the appendix to this letter, empagliflozin meets the requirement of established medical science and medical practice for treating GSD-Ib and GSD-XI.

Budget impact analysis
Expanding the List 2 conditions for empagliflozin is not expected to be accompanied by additional costs for the pharmaceutical budget, due to the very low numbers of patients with GSD-Ib and GSD-XI in the Netherlands, combined with the cost savings associated with the large price difference between colony-stimulating factors (G-CSF) and empagliflozin. The National Health Care Institute has therefore not carried out a budget impact analysis.

Advice
Empagliflozin has been included on List 1A of the GVS (cluster 0A10BXAO V) with further conditions. Given the above reasoning, the National Health Care Institute advises you to expand the List 2 conditions as follows:

Condition: For an insured person with glycogen storage disease type Ib and for an insured person with glycogen storage disease type XI

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board

Enclosed: Pharmacotherapeutic assessment

Pharmacotherapeutic assessment

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Background

Glycogen storage disease type Ib (GSD-Ib)
Glycogen storage disease type Ib (GSD-Ib; Von Gierke disease) is a rare hereditary disorder of the carbohydrate metabolism. The breakdown of glycogen is disrupted. This leads to accumulation of glycogen and fat, particularly in the liver and kidneys. The disorder is caused by mutations in the SLC37A4 gene that lead to a deficit in the glucose-6-phosphate transporter (G6PT). The clinical phenotype is typified by intolerance to fasting, hepatomegaly and hepatosplenomegaly, as well as symptoms of neutropenia and neutrophil dysfunction such as infections, ulcers throughout the gastrointestinal system, and inflammatory bowel diseases. Without treatment, the patients die at a young age. With treatment, growth and puberty can be expected to proceed normally and the majority of patients reach adulthood.[1, 2]

The exact prevalence of GSD-Ib is unknown. It is estimated that 1 person in 100,000 has GSD-I, of which 20% are subtype Ib[1]. The overall prevalence of patients with GSD-Ib in the Netherlands is 18, according to the Dutch Diagnosis Registration Metabolic Diseases (DDRMD).[3]

Glycogen storage disease type XI (GSD-XI)
Glycogen storage disease type XI (GSD-XI) is a rare hereditary disorder of the carbohydrate metabolism. It is caused by dysfunctional variants of the SLC2A2 gene, which codes for the GLUT2 transporter in hepatocytes, pancreatic beta cells and the membranes of intestinal epithelial cells and cells in the proximal tubuli of the kidneys. GLUT2 moves glucose in or out of the cell using a passive transport mechanism. Disruption of glucose homeostasis and generalised proximal tubulopathy mean that GSD-XI can lead to severe polyuria and severe rachitis with growth retardation.[4]

GSD-XI is a very rare disease. Its prevalence is unknown. As yet, fewer than 200 cases have been described in the literature.[5] There are currently 3 patients with GSD-XI in the Netherlands.

Empagliflozin
Empagliflozin inhibits the sodium-glucose cotransporter 2 (SGLT2) and thereby the reabsorption of glucose in the kidneys. This leads to excretion of glucose in the urine and osmotic diuresis. As a result, the neutropenia and neutrophil dysfunction in GSD-Ib improve.[2]

SGLT2 inhibitors such as empagliflozin[1] are also thought to be able to improve renal function in patients with GSD-XI by the same mechanism, as demonstrated by Trepiccione *et al.* in a mouse model.[6]

[1] A class effect could be involved. The professional group has chosen to use empagliflozin for these very rare conditions to acquire as much experience as possible and to document the results.

Guidelines

Treatment of glycogen storage disease type Ib (GSD-Ib)
Treatment of patients with GSD-Ib in the Netherlands is described in the care path for glycogen storage disease type I that was drawn up in 2021 by the Expertise Centre at UMCG, the Academic Medical Center in Amsterdam, the University Medical Centre in Utrecht, and the VKS.[1] There are also international treatment recommendations for using empagliflozin in GSD-Ib (2024).[7]

The foundation for treating GSD-Ib consists of a medically prescribed, personalised diet. If the treatment goals are not achieved despite this diet, medical management follows. Drugs that are frequently used for this are xanthine oxidase inhibitors, lipid-lowering drugs, fibrates, ACE inhibitors (angiotensin-converting enzyme), angiotensin II antagonists, citrate, vitamins and minerals, and iron preparations. Additionally, these patients are specifically treated with prophylactic antibiotics (co-trimoxazole) and granulocyte colony-stimulating factor (G-CSF). However, G-CSF does not completely restore the neutrophil function. In the longer term, using G-CSF can have severe side effects (such as splenomegaly and haematological malignancies). On top of that, the treatment with subcutaneous injections is painful, invasive, expensive and impractical, given that the injections have to be transported and stored cold.

According to the prescribed care path, recent scientific literature has indications for treating symptoms of neutropenia and neutrophil dysfunction in patients with GSD-Ib with an SGLT2 inhibitor such as empagliflozin. Given that this is still an experimental off-label treatment, the indications, outcomes and possible side effects should be monitored closely on an individual basis. Where there is neutropenia and neutrophil dysfunction, starting with an SGLT2 inhibitor such as empagliflozin can be considered before moving on to G-CSF treatment.

The international treatment recommendations advise phasing down G-CSF in all patients 2 to 4 weeks after starting empagliflozin, in particular if the neutrophil count is normal. In patients who no longer have symptoms when being treated with empagliflozin, it is recommended that additional treatments for neutropenia, neutrophil dysfunction and inflammatory bowel diseases should be discontinued.[7]

Treatment of glycogen storage disease type XI (GSD-XI)
There are no Dutch or international guidelines for treating GSD-XI. As with GSD-Ib, patients with GSD-XI are treated with a diet and medicines. Many supplements have unpleasant tastes, however, and may cause abdominal pain and need to be administered several times a day. Compliance with the therapy and the diet are important, particularly during childhood because that period is crucial for growth and development.[4]

Favourable effects on GSD-Ib

Description of the study
The effectiveness and safety of empagliflozin in patients with GSD-Ib have been investigated in a retrospective questionnaire study among healthcare professionals in 24 countries throughout the world. Clinical data from 112 patients with GSD-Ib were gathered and anonymised. The median age at the start of treatment with empagliflozin was 10.5 years (average 12.8; range 0-38), 71% of the patients were younger than 18. The median duration of treatment was 9.5 months (average 10.5; range 1-27). The median empagliflozin dose was 0.35 mg/kg/day.[8]

The effect of empagliflozin on patient-reported outcome measures (PROMs) and the quality of life (QoL) was investigated in a questionnaire study among 73 patients and carers of patients (including paediatric patients) from 17 countries. The median age of the patients was 11 years (range 0-48). Treatment with empagliflozin was started at a median age of 10 years (range 0-47). The median duration of treatment was 9.5 months (range 2-36). The daily dose of empagliflozin was between 0.05 and 1.9 mg/kg/day with a median dose of 0.36 mg/kg/day.[9]

Clinical measures of outcome
Table 1 gives an overview of the symptoms of neutropenia and neutrophil dysfunction from the questionnaire study among healthcare professionals. Empagliflozin had a positive effect on all these symptoms.[8]

Table 1. Clinical measures of outcome before and during treatment with empagliflozin[8]

	Before treatment with empagliflozin	**During treatment with empagliflozin**
Neutropenia		
Severe (ANC <500/µL)	29% (32/112)	10% (11/108)
Moderate (ANC 500-1000/µL)	41% (46/112)	22% (24/108)
Mild (ANC 1000-1500/µL)	13% (15/112)	15% (16/108)
None	17% (19/112)	53% (57/108)
Relapses of oral/anogenital mucosal lesions	68% (76/112)	13% (14/109)[a]
Relapses of bacterial/skin infections	54% (61/112)	8% (9/109)[a]
Inflammatory bowel diseases		
Severe	10% (11/110)	0% (0/106)
Moderate	27% (30/110)	6% (6/106)
Mild	23% (25/110)	16% (17/106)
None	40% (44/110)	78% (83/106)
Anaemia		
Required erythrocyte transfusions	4% (5/112)	0% (0/110)
Required treatment with iron	37% (41/112)	16% (18/110)
Did not require intervention	32% (36/112)	14% (15/110)
None	27% (30/112)	70% (77/110)

ANC, absolute neutrophil count
[a] Milder, rarer and less painful than before

In the questionnaire study among patients and carers, a large majority of the patients responded well to treatment with empagliflozin, showing clear improvements in the symptoms of neutropenia and neutrophil dysfunction. The neutropenia disappeared in 95% of the patients. Half the patients (50%) reported an improvement in severe hypoglycaemia during treatment with empagliflozin. Of the 73 patients, 62 (85%) reported no problems maintaining normal blood glucose values. In 15% (11/73), however, an increase in the number of hypoglycaemic episodes was observed compared with the period preceding the treatment with empagliflozin.

Stopping or reducing treatment with G-CSF
Of the 112 patients in the study among healthcare professionals, data about the use of G-CSF after starting empagliflozin was available for 107. Of those, 89 were treated with G-CSF before starting on empagliflozin. Treatment with empagliflozin meant that 49 of those 89 patients (55%) were able to stop G-CSF. The G-CSF dose could be lowered significantly in 15 of the 89 patients (17%).[8]

Of the 73 patients in the study using PROMs and QoL, 66 (90%) were receiving G-CSF before starting on empagliflozin. Two of those 66 patients did not respond to questions about the follow-up. Treatment with G-CSF was discontinued in 35 of the 71 patients (49%) after starting on empagliflozin. It was possible to reduce the G-CSF dose or frequency of administration or both in 30 of the 71 patients (42%). The G-CSF dose or frequency of administration or both could not be reduced in 6 of the 71 patients (7%), or no attempt was made to do so.[9]

Quality of life (QoL)
In the study among patients and carers, empagliflozin had a positive effect on appetite, physical performance and activity, the general well-being of the patient and carers, and on sleep for the patient and carers. The number of hospital admissions was reduced in 66% of the patients (48/73).[9]

82% (60/3) of the patients felt that their QoL had improved; the QoL was unchanged in 10% (7/73) and 8% (6/73) reported that it had worsened. This was reflected in a significant change in the average QoL score from 4.3 before treatment to 2.2 after treatment with empagliflozin.[9]

The majority of the patients/carers stated that leading their daily lives became easier after the start of treatment with empagliflozin (average score 2.18 on a scale from 1 = *definitely* to 7 = *definitely not*). Fewer days of illness were reported by 67% of patients (49/73) and 27% of the carers of paediatric patients (12/44). Patients who were treated with empagliflozin assessed the overall improvement in their daily lives very positively.[9]

Other considerations
In the study among healthcare professionals, the effectiveness of empagliflozin was comparable for paediatric and adult patients.[8]

In the study among patients and carers, the burden of the daily G-CSF injections was experienced very differently. Patients who were able to discontinue G-CSF or who could lower the dose or dosage frequency perceived this as a great relief.[9]

The effect of empagliflozin on the PROMs and the clinical and pharmacoeconomic measures of outcome respectively was also examined in 11 Dutch and Austrian patients with GSD-Ib in a small-scale, retrospective, non-interventional study. Seven of the eleven patients (64%) could discontinue G-CSF thanks to the treatment with empagliflozin and the dose of G-CSF could be reduced in the other four. The neutrophil count increased in 8 of the 11 patients (73%) and remained within a normal range in 6 of the 11 (55%). All the patients showed a significant improvement in the symptoms related to neutropenia and neutrophil dysfunction. QoL data was available for 8 of the 11 patients and it showed an improvement in all cases. According to the patients and their carers, the treatment with empagliflozin led to a positive effect on ulcers and diarrhoea. The time between meals could be extended. Needing fewer injections of G-CSF was perceived as highly valuable by both the patients and their parents. In addition, the fact that empagliflozin does not have to be transported and stored cooled made a big difference.[2]

Favourable effects on GSD-XI

Description of the study
A case report describes the effectiveness and safety of empagliflozin in 7 patients with GSD-XI in 3 hospitals (one in the Netherlands and two in Germany). The cohort comprised 5 men (71%) and 2 women (29%). The median age (and range) at the start of treatment with empagliflozin was 27 years (1-61) and the median follow-up duration on empagliflozin was 169 days (57-344). As with GSD-Ib, the initial dose was low (0.3-0.4 mg/kg/day for children of <25 kg, or 10 mg/day for children of >25 kg and adults) and it was then increased to a maximum of 0.8 mg/kg/day for children or 20-25 mg/day for adults. Clinical and biochemical data was obtained retrospectively from the medical notes.[4]

Clinical measures of outcome
Improvements in glucose homeostasis were seen in all four GSD-XI patients who were using CGM. All three children were able to stop taking supplements entirely (various combinations of phosphate, alkali, carnitine and alfacalcidol) after 1 week, 3 months and 8 months respectively. Stopping those also improved their therapy compliance.[4]

Biochemical measures of outcome
All the patients in the study showed improved biochemical parameters for tubule cell integrity and/or tubule function, albeit to varying degrees.[4]

Other considerations
Given that this study was carried out retrospectively, there is a risk of recall bias. For the same reason, some biochemical parameters were missing for some patients too. The median follow-up duration for the study was short, at just 169 days. There was also considerable heterogeneity between the patients. This confirms the need for an individualised, multidisciplinary approach to GSD-XI.

In this study, only the paediatric patients were able to discontinue using supplements. Inhibition of glucose reabsorption may possibly have been too low, or the follow-up duration of the study too short to allow the treatment with supplements to be phased out in adults. The damage to the renal tubuli may also possibly be more severe in adults, or perhaps even irreversible. A third reason could be that these patients have an elevated blood glucose concentration, reducing the effect of empagliflozin. Finally, there could also be a genetic cause.[4]

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Undesirable effects

Side-effect profile
In the summary of product characteristics (SmPC), the side-effect profile of empagliflozin is based on studies in patients with diabetes mellitus type 2, heart failure and chronic renal damage.[10] According to the SmPC, the very common (≥1/10) side effects are hypoglycaemia (when used with a sulfonylurea derivative or insulin) and volume depletion. Common side effects (≥1/100, <1/10) are vaginal candidiasis, vulvovaginitis, balanitis and other genital infections, urinary tract infections (including pyelonephritis and urosepsis), thirst, constipation, itching, rash, more frequent urination and elevated serum lipids. Less common side effects are ketoacidosis, urticaria, angioedema, dysuria, elevated blood creatinine, lowered glomerular filtration rate, elevated haematocrit, necrotising fasciitis of the perineum and tubulointerstitial nephritis.

GSD-Ib
In 69% of the patients (77/112) in the study among healthcare professionals, no undesirable effects were reported; in 21% (23) there was a single undesirable effect; in 5% (6) there were two undesirable effects; and in 3% (3) there were three undesirable effects. The proportion of the undesirable effects that were related to the intervention was not reported. The most common undesirable effect was grade 3 hypoglycaemia. This occurred in 18% (20/111) of all patients. This led to 9 patients requiring intramural treatment and 11 extramural. The most severe undesirable effect was lactic acidosis, which was reported in 6 patients, of whom 5 were admitted to hospital. One of the adult patients also had significant ketoacidosis. In another adult patient, 2 decompensations were reported that required admission to intensive care; both were associated with gastroenteritis and dehydration.

Hypoglycaemia and lactic acidosis are typical clinical symptoms of GSD-Ib. The cause of these undesirable effects is therefore difficult to determine. Because the glucose values are strictly monitored and also adjusted using dietary therapy, the professional group does not see hypoglycaemia as a possible negative effect.[8]

As stated earlier, an increase in the number of hypoglycaemic episodes compared with the period preceding the treatment with empagliflozin was observed in 15% (11/73) of the patients in the study among patients and carers. Other than hypoglycaemia, 75% of the patients (55/73) did not report any undesirable effects. The other undesirable effects, which were mentioned by 18 patients, are not severe and were only reported once, except for weight gain (n=3), urinary tract infections (n=2) and night-time thirst (n=2).[9] Hypoglycaemia was seen about equally often in adults (14%) as in patients aged <18 (18%). For all the other undesirable effects, the size of the study was too small to allow reliable conclusions to be drawn.[8]

GSD-XI
Empagliflozin was well tolerated in the study with GSD-XI patients. No undesirable effects were reported by the patients or carers. No symptomatic hypoglycaemia or hypotension was observed either.

Conclusion

The effectiveness and safety of empagliflozin in patients with GSD-Ib have been investigated in two questionnaire studies, one among healthcare professionals and one among patients and their carers. The situation before starting on empagliflozin was compared against the situation afterwards. Empagliflozin not only improved neutropenia in patients with GSD-Ib but also had a positive effect on all symptoms of neutropenia and neutrophil dysfunction such as infections, ulcers throughout the gastrointestinal system, and inflammatory bowel diseases. Almost all patients were able to reduce the dose of G-CSF or discontinue it when treated with empagliflozin. Empagliflozin had an acceptable side-effect profile and improved the QoL of patients with GSD-Ib.

The effectiveness and safety of empagliflozin in GSD-XI have been described in a case report covering 7 patients. Empagliflozin can reduce the symptoms of proximal renal tubulopathy in these patients, particularly when the treatment begins in early childhood. Empagliflozin was well tolerated in this study.

Based on the favourable and unfavourable effects and given that GSD-Ib and GSD-XI are extremely rare conditions with just a handful of patients in the Netherlands, the National Health Care Institute deems the outcomes of the questionnaire studies to be sufficient and appropriate evidence for concluding that empagliflozin complies with the criterion of established medical science and medical practice for treating GSD-Ib and GSD-XI.

Recommendation in the *Farmacotherapeutisch Kompas*
Off label: The symptoms of neutropenia and neutrophil dysfunction in GSD-Ib patients can be treated with empagliflozin. The indications, outcomes and possible side effects should be monitored closely on an individual basis. Where there is neutropenia and neutrophil dysfunction, starting with empagliflozin can be considered before moving on to treatment with granulocyte colony-stimulating factor (G-CSF).

Off label: The symptoms of proximal renal tubulopathy in GSD-XI patients can be treated with empagliflozin. The indications, outcomes and possible side effects should be monitored closely on an individual basis.

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