Patiromer
(hyperkalaemia in children and adolescents)

Benefit assessment according to §35a SGB V[1]

EXTRACT

Project: A24-14 Version: 1.0 Status: 22 Apr 2024 DOI: 10.60584/A24-14_en

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Patiromer (Hyperkaliämie bei Kindern und Jugendlichen) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Patiromer (hyperkalaemia in children and adolescents) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

1 February 2024

Internal Project No.

A24-14

DOI-URL

https://doi.org/10.60584/A24-14_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Wolfgang Rascher, Paediatric and Adolescent Clinic, University of Erlangen-Nuremberg, Erlangen, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Michael Köhler
- Benjamin Becker
- Deborah Ingenhag-Reister
- Maximilian Kind
- Daniela Preukschat
- Veronika Schneck
- Dorothea Sow
- Kathrin Wohlhöfner

Keywords

Patiromer, Hyperkalemia, Child, Adolescent, Benefit Assessment

Part I: Benefit assessment

I Table of contents

I List of tables[2]

Page

[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AMG	Arzneimittelgesetz (Medicinal Products Act)
CaPSS	calcium polystyrene sulfonate
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
mEq	milliequivalent
NaPSS	sodium polystyrene sulfonate
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug patiromer. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 01 February 2024.

Research question

The aim of this report is to assess the added benefit of patiromer compared with polystyrene sulfonates (calcium-polystyrene sulfonate [CaPSS] or sodium polystyrene sulfonate [NaPSS]) as appropriate comparator therapy (ACT) in children and adolescents aged 12 years and older with hyperkalaemia.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of patiromer

Therapeutic indication	**ACT**[a]
Children and adolescents aged 12 years and older with hyperkalaemia[b]	Polystyrene sulfonates (CaPSS or NaPSS)

a. Presented is the ACT specified by the G-BA.
b. It is assumed that the patients in the present therapeutic indication do not have potentially life-threatening hyperkalaemia requiring emergency treatment. Other therapeutic measures are available for emergency treatment. Furthermore, it is assumed that general interventions to normalize serum potassium levels (optimization of the treatment of underlying and accompanying diseases, in particular the adjustment of drug therapy and, if necessary, a change in diet) are carried out first in the patient population with hyperkalaemia. Only if these attempts are unsuccessful and hyperkalaemia requiring intervention persists is specific drug treatment for hyperkalaemia considered. This applies to the use of patiromer as well as polystyrene sulfonates.

ACT: appropriate comparator therapy; CaPSS: calcium-polystyrene sulfonate; G-BA: Joint Federal Committee; NaPSS: sodium polystyrene sulfonate

The company did not follow the G-BA's specification of the ACT. In the company's view, the polystyrene sulfonates (CaPSS and NaPSS) do not adequately represent the appropriate comparator therapy (ACT) for the paediatric population. The company refers to the previous benefit assessments for patiromer and sodium zirconium cyclosilicate (the therapeutic indication in each case refers to adult patients with hyperkalaemia), for each of which the G-BA determined an individualized treatment of physician's choice. According to the company, the recommendations in current guidelines on the management of hyperkalaemia also reflect individualized treatment of physician's choice and polystyrene sulfonates are only recommended to a limited extent or not at all for drug treatment. In addition, the company states that the polystyrene sulfonates CaPSS and NaPSS were approved before the Medicinal

Products Act (AMG) came into force and that there is a lack of evidence-based data for the approval of these substances, particularly for the treatment of hyperkalaemia in children.

The company's deviation from the ACT specified by the G-BA will not be further commented below, as the company did not present any suitable data for the benefit assessment – neither compared with a comparator therapy designated by the company nor compared with the ACT specified by the G-BA. The present assessment is carried out in comparison with the G-BA's ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

Results

No relevant study was identified from the check of the completeness of the study pool.

The company included the single-arm study EMERALD in its benefit assessment and stated that it presented the results of this study descriptively as the best available evidence. Children aged 2 to 17 years with chronic kidney disease and hyperkalaemia with a serum potassium level of 5.1 to < 6.5 milliequivalents (mEq)/L were to be included in the study. Patients should be expected to require treatment for hyperkalaemia for at least 6 months. The study comprised 3 age cohorts, whereby 14 patients were included in the cohort of patients aged 12 to 17 years relevant for the present evaluation. All patients were treated with patiromer. The treatment was carried out over a total of 26 weeks, with the first 14 days serving for individual dose finding. The primary outcome was the change in serum potassium levels from baseline to day 14. Adverse events were also recorded as further outcomes.

As the EMERALD study did not provide a comparison with the G-BA's ACT, the study is not suitable for the benefit assessment.

Results on added benefit

There are no suitable data available for the assessment of added benefit of patiromer for the treatment of children and adolescents aged 12 years and older with hyperkalaemia compared to the ACT. There is no hint of an added benefit of patiromer in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of probability and extent of the added benefit of patiromer.

Table 3: Patiromer – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Children and adolescents aged 12 years and older with hyperkalaemia	Polystyrene sulfonates (CaPSS or NaPSS)[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. It is assumed that the patients in the present therapeutic indication do not have potentially life-threatening hyperkalaemia requiring emergency treatment. Other therapeutic measures are available for emergency treatment. Furthermore, it is assumed that general interventions to normalize serum potassium levels (optimization of the treatment of underlying and accompanying diseases, in particular the adjustment of drug therapy and, if necessary, a change in diet) are carried out first in the patient population with hyperkalaemia. Only if these attempts are unsuccessful and hyperkalaemia requiring intervention persists is specific drug treatment for hyperkalaemia considered. This applies to the use of patiromer as well as polystyrene sulfonates.

ACT: appropriate comparator therapy; CaPSS: calcium-polystyrene sulfonate; G-BA: Joint Federal Committee; NaPSS: sodium polystyrene sulfonate

The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

I 2 Research question

The aim of this report is to assess the added benefit of patiromer compared with polystyrene sulfonates (calcium-polystyrene sulfonate [CaPSS] or sodium polystyrene sulfonate [NaPSS]) as appropriate comparator therapy (ACT) in children and adolescents aged 12 years and older with hyperkalaemia.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of patiromer

Therapeutic indication	**ACT**[a]
Children and adolescents aged 12 years and older with hyperkalaemia[b]	Polystyrene sulfonates (CaPSS or NaPSS)

a. Presented is the ACT specified by the G-BA.
b. It is assumed that the patients in the present therapeutic indication do not have potentially life-threatening hyperkalaemia requiring emergency treatment. Other therapeutic measures are available for emergency treatment. Furthermore, it is assumed that general interventions to normalize serum potassium levels (optimization of the treatment of underlying and accompanying diseases, in particular the adjustment of drug therapy and, if necessary, a change in diet) are carried out first in the patient population with hyperkalaemia. Only if these attempts are unsuccessful and hyperkalaemia requiring intervention persists is specific drug treatment for hyperkalaemia considered. This applies to the use of patiromer as well as polystyrene sulfonates.

ACT: appropriate comparator therapy; CaPSS: calcium-polystyrene sulfonate; G-BA: Joint Federal Committee; NaPSS: sodium polystyrene sulfonate

The company did not follow the G-BA's specification of the ACT. In the company's view, the polystyrene sulfonates (CaPSS and NaPSS) do not adequately represent the ACT for the paediatric population. The company refers to the previous benefit assessments for patiromer and sodium zirconium cyclosilicate (the therapeutic indication in each case refers to adult patients with hyperkalaemia), for each of which the G-BA determined an individualized treatment of physician’s choice [3,4]. According to the company, the recommendations in current guidelines on the management of hyperkalaemia also reflect individualized treatment of physician’s choice and polystyrene sulfonates are only recommended to a limited extent or not at all for drug treatment [5-8]. In addition, the company states that the polystyrene sulfonates CaPSS and NaPSS were approved before the AMG came into force and that there is a lack of evidence-based data for the approval of these substances, particularly for the treatment of hyperkalaemia in children.

The company’s deviation from the ACT specified by the G-BA will not be further commented below, as the company did not present any suitable data for the benefit assessment – neither compared with a comparator therapy designated by the company nor compared with the ACT specified by the G-BA. The present assessment is carried out in comparison with the G-BA’s ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on patiromer (status: 17 November 2023)
- bibliographical literature search on patiromer (last search on 16 November 2023)
- search in trial registries/trial results databases for studies on patiromer (last search on 17 November 2023)
- search on the G-BA website for patiromer (last search on 16 November 2023)

To check the completeness of the study pool:

- search in trial registries for studies on patiromer (last search on 14 February 2024); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, no RCT on the direct comparison of patiromer versus the ACT was identified from the check.

As the company did not identify any RCT for the direct comparison of patiromer in comparison with the ACT, it conducted an information retrieval for further investigations on patiromer. It identified the single-arm study EMERALD. The company has conducted no information retrieval on other investigations for the ACT.

The data presented by the company are unsuitable for drawing conclusions on the added benefit of patiromer in comparison with the ACT. This is justified below. The completeness of the study pool for further investigations was not checked.

Evidence provided by the company

The company included the single-arm study EMERALD [9,10] in its benefit assessment and stated that it presented the results of this study descriptively as the best available evidence. Children aged 2 to 17 years with chronic kidney disease and hyperkalaemia with a serum potassium level of 5.1 to < 6.5 mEq/L were to be included in the study. Patients should be expected to require treatment for hyperkalaemia for at least 6 months. The study comprised 3 age cohorts, whereby 14 patients were included in the cohort of patients aged 12 to 17 years relevant for the present evaluation. All patients were treated with patiromer. Within the relevant age cohort, 3 different starting doses should be used (4.2 mg/day, 8.4 mg/day and 16.8 mg/day). The study documents show that 13 patients in this age cohort received a starting dose of 4.2 g/day. The treatment was carried out over a total of 26 weeks, with the first 14 days serving for individual dose finding. The patiromer dose was to be titrated up

during the course of treatment in such a way that a serum potassium level of 3.8 to 5.0 mEq/L was achieved. From week 3 to week 26, the dose could be individually increased or decreased to maintain the target potassium level. The maximum dose in the relevant age cohort was 25.2 g/day throughout the duration of the study. The primary outcome was the change in serum potassium levels from baseline to day 14. Adverse events were also recorded as further outcomes.

As the EMERALD study did not provide a comparison with the G-BA's ACT, the study is not suitable for the benefit assessment.

I 4 Results on added benefit

There are no suitable data available for the assessment of added benefit of patiromer for the treatment of children and adolescents aged 12 years and older with hyperkalaemia compared to the ACT. There is no hint of an added benefit of patiromer in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of patiromer in comparison with the ACT is summarized in Table 5.

Table 5: Patiromer – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Children and adolescents aged 12 years and older with hyperkalaemia	Polystyrene sulfonates (CaPSS or NaPSS)[b]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. It is assumed that the patients in the present therapeutic indication do not have potentially life-threatening hyperkalaemia requiring emergency treatment. Other therapeutic measures are available for emergency treatment. Furthermore, it is assumed that general interventions to normalize serum potassium levels (optimization of the treatment of underlying and accompanying diseases, in particular the adjustment of drug therapy and, if necessary, a change in diet) are carried out first in the patient population with hyperkalaemia. Only if these attempts are unsuccessful and hyperkalaemia requiring intervention persists is specific drug treatment for hyperkalaemia considered. This applies to the use of patiromer as well as polystyrene sulfonates.

ACT: appropriate comparator therapy; CaPSS: calcium-polystyrene sulfonate; G-BA: Joint Federal Committee; NaPSS: sodium polystyrene sulfonate

The assessment described above concurs with that of the company.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 06.10.2023]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Patiromer (Hyperkaliämie) [online]. 2018. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/356/.

4. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Natrium-Zirkonium-Cyclosilikat (Hyperkaliämie) [online]. 2021. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/669/.

5. Cheung AK, Chang TI, Cushman WC et al. KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Kidney Int 2021; 99(3): S1-S87. https://doi.org/10.1016/j.kint.2020.11.003.

6. McDonagh TA, Metra M, Adamo M et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2021; 42(36): 3599-3726. https://doi.org/10.1093/eurheartj/ehab368.

7. Rossing P, Caramori ML, Chan JCN et al. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int 2022; 102(5): S1-S127. https://doi.org/10.1016/j.kint.2022.06.008.

8. Mancia G, Kreutz R, Brunström M et al. 2023 ESH Guidelines for the management of arterial hypertension. J Hypertens 2023; 41(12): 1874-2071. https://doi.org/10.1097/hjh.0000000000003480.

9. Vifor Pharma. A Phase 2, Open-Label, Multiple Dose Study to Evaluate the Pharmacodynamic Effects, Safety, and Tolerability of Patiromer for Oral Suspension in Children and Adolescents 2 to < 18 Years of Age with Chronic Kidney Disease and Hyperkalemia (EMERALD) [online]. [Accessed: 21.02.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-002785-31.

10. Vifor Pharma. Pharmacodynamic & Safety of Patiromer in Children & Adolescents (2-<18 Yrs) With Chronic Kidney Disease and Hyperkalemia (EMERALD) [online]. 2022 [Accessed: 21.02.2024]. URL: https://clinicaltrials.gov/study/NCT03087058.

The full report (German version) is published under https://www.iqwig.de/en/projects/a24-14.html.