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Sodium zirconium cyclosilicate (hyperkalaemia) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Natriumzirkoniumcyclosilicat (Hyperkaliämie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 June 2021). 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.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug sodium zirconium cyclosilicate. 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 1 April 2021.

Research question

The aim of this report is to assess the added benefit of sodium zirconium cyclosilicate in comparison with the appropriate comparator therapy (ACT) in adult patients with hyperkalaemia.

The G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of sodium zirconium cyclosilicate

Indication	ACT[a]
Adult patients with hyperkalaemia[b]	Individualized therapy upon the physician's discretion, taking into account aetiology, severity, and symptoms. Individualized therapy measures which represent the standard therapy of hyperkalaemia include treatment optimization for underlying diseases and comorbidities, particularly adaptation of drug therapy and, if necessary, a change in diet.[c]
a. Presented is the respective ACT specified by the G-BA. b. The G-BA assumes that patients in the present therapeutic indication do not suffer from potentially life-threatening hyperkalaemia which would require rescue therapy. Different therapeutic measures are available for rescue therapy. c. According to the G-BA, any planned studies must provide for adaptation of standard therapy in the comparator arm. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company generally followed the ACT specified by the G-BA by likewise specifying individualized therapy upon the physician's discretion as the ACT. However, the company distinguished 3 treatment situations, specifically correction phase, maintenance phase, and patients requiring dialysis. The company based this breakdown on the Summary of Product Characteristics (SPC) specifying different dosages and administration methods for these treatment situations. For each of these 3 treatment situations, the company defined specific therapies to be deemed individualized therapy upon the physician's discretion.

However, differing dosage specifications do not justify breaking down the research question into 3 treatment situations.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for deriving any added benefit.

Results

For adult patients with hyperkalaemia, no relevant RCT directly comparing sodium zirconium cyclosilicate with the ACT was found. Due to failure to implement the ACT and a short study duration, the 5 RCTs submitted by the company (DIALIZE, ZS-002, D9482C00002, ZS-003, ENERGIZE) are unsuitable for deriving any added benefit. This results in no hint of added benefit of sodium zirconium cyclosilicate in comparison with the ACT for adult patients with hyperkalaemia; an added benefit is therefore not proven.

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

Table 3 presents a summary of the probability and extent of added benefit of sodium zirconium cyclosilicate.

Table 3: Sodium zirconium cyclosilicate – probability and extent of added benefit

Indication	ACT[a]	Probability and extent of added benefit
Adult patients with hyperkalaemia[b]	Individualized therapy upon the physician's discretion, taking into account aetiology, severity, and symptoms. Individualized therapy measures which represent the standard therapy of hyperkalaemia include treatment optimization for underlying diseases and comorbidities, particularly adaptation of drug therapy and, if necessary, a change in diet.[c]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. The G-BA assumes that patients in the present therapeutic indication do not suffer from potentially life-threatening hyperkalaemia which would require rescue therapy. Different therapeutic measures are available for rescue therapy.
c. According to the G-BA, any planned studies must provide for adaptation of standard therapy in the comparator arm.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

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].

2.2 Research question

The aim of this report is to assess the added benefit of sodium zirconium cyclosilicate in comparison with the ACT in adult patients with hyperkalaemia.

The G-BA's specification of the ACT results in the research question presented in Table 4.

Table 4: Research question of the benefit assessment of sodium zirconium cyclosilicate

Indication	**ACT**[a]
Adult patients with hyperkalaemia[b]	Individualized therapy upon the physician's discretion, taking into account aetiology, severity, and symptoms. Individualized therapy measures which represent the standard therapy of hyperkalaemia include treatment optimization for underlying diseases and comorbidities, particularly adaptation of drug therapy and, if necessary, a change in diet.[c]
a. Presented is the respective ACT specified by the G-BA. b. The G-BA assumes that patients in the present therapeutic indication do not suffer from potentially life-threatening hyperkalaemia which would require rescue therapy. Different therapeutic measures are available for rescue therapy. c. According to the G-BA, any planned studies must provide for adaptation of standard therapy in the comparator arm. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company generally followed the ACT specified by the G-BA by likewise specifying individualized therapy upon the physician's discretion as the ACT. However, in its research question, the company distinguished the following 3 treatment situations: correction phase, maintenance phase, and patients requiring dialysis. The company based this breakdown on the different dosages and administration methods specified for these treatment situations in the SPC [3]. For each of these 3 treatment situations, the company defined specific therapies to be deemed individualized therapy upon the physician's discretion.

However, differing dosage specifications do not justify breaking down the research question into 3 treatment situations. In particular, it is inappropriate to assess the correction phase separately from the maintenance phase. The treatment concept of hyperkalaemia comprises both phases (correction and maintenance phase). Moreover, the ACT addressed under this research question represents individualized therapy upon the physician's discretion for the entire target population. The fact that the employed therapies differ depending on aetiology, severity, and symptoms for individual patients or patient groups (e.g. patients requiring dialysis and those not requiring dialysis) has already been taken into account. Therefore, it is not necessary to break down the research question by treatment situation.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for deriving any added benefit. This concurs with the approach used by the company for the treatment situation of maintenance therapy. The company used different treatment durations

as inclusion criteria for the other treatment situations, namely a maximum of 72 hours for the correction phase and at least 4 weeks for patients requiring dialysis.

2.3 Information retrieval and study pool

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

Sources cited by the company in the dossier:

- Study list on sodium zirconium cyclosilicate (as of 24 March 2021)
- Bibliographic literature search on sodium zirconium cyclosilicate (most recent search on 12 February 2021)
- Search in trial registries / study results databases on sodium zirconium cyclosilicate (most recent search on 1 February 2021)
- Search on the G-BA website on sodium zirconium cyclosilicate (most recent search on 16 February 2021)

To check the completeness of the study pool:

- Search in trial registries for studies on sodium zirconium cyclosilicate (most recent search on 22 April 2021); see Appendix B of the full dossier assessment for the search strategies.

No relevant study was identified from the check.

Evidence provided by the company

The company submitted a total of 5 RCTs: DIALIZE, which the company submitted for its analysis of the patient population requiring dialysis, as well as ENERGIZE, D9482C00002, ZS-002 and ZS-003, which the company submitted for its analysis of the treatment situation of correction phase. The company did not identify any study for the treatment situation of maintenance phase. Data on study characteristics and on the interventions used in the studies are presented in Appendix A of the full dossier assessment.

Irrespective of the consideration of the 3 treatment situations, these 5 RCTs are unsuitable for deriving any added benefit of sodium zirconium cyclosilicate in the present benefit assessment. The reasons are explained below.

ACT not implemented in the studies

In all 5 studies submitted by the company, sodium zirconium cyclosilicate was compared to placebo rather than to the ACT. The studies either disallowed individualized therapy – e.g. through adaptation of the drug therapy to treat underlying diseases or comorbidities – or adaptation led to discontinuation of the study drug or was possible only to a very limited extent (e.g. as rescue therapy).

The 10-week DIALIZE study [4-6], which investigated dialysis patients, specified nutritional counselling as individualized therapy for patients, albeit allowing adjustment of the dialysate potassium concentration only in the first 4 weeks if necessary. In case of severe hyperkalaemia, initiating rescue therapy was also possible.

In the 3-week study ZS-003 [7,8], all concomitant medications were to be continued at a constant dose over the course of the study. This study allowed rescue therapies for acute hypokalaemia or hyperkalaemia, but they led to discontinuation of the study drug.

Few data are available on the concomitant medication used in the 1-week study ZS-002 [9,10]. The previously prescribed medication was to be continued. However, dietary changes were explicitly not called for [10]. In addition, no information is available as to which options, if any, there were to initiate rescue therapy if necessary.

The 9-day study D9482C00002 [11] disallowed any drugs other than the study drug for treating hyperkalaemia.

The 8-day study ENERGIZE [12,13] called for the administration of insulin + glucose alongside the study drug, but potassium-lowering drugs (e.g. potassium binders such as patiromer) were allowed only as rescue therapy.

Insufficient study duration

In addition to failing to implement the ACT, the 5 studies included by the company are of insufficient duration. No conclusions on long-term adverse events can be drawn on the basis of the submitted studies. In Module 4 A, the company does point out that for the benefit assessment of sodium zirconium cyclosilicate, like for the comparable benefit assessment of patiromer [14], the G-BA requires a 24-week study duration specified for chronic diseases.

In summary, for the cited reasons, none of the 5 RCTs included by the company (DIALIZE, ZS-002, D9482C00002, ZS-003, ENERGIZE) is relevant for the present benefit assessment.

2.4 Results on added benefit

The company did not present any suitable data for assessing any added benefit of sodium zirconium cyclosilicate in comparison with the ACT for the treatment of adult patients with hyperkalaemia. Consequently, there is no hint of added benefit of sodium zirconium cyclosilicate in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

No suitable data are available for the assessment of added benefit of sodium zirconium cyclosilicate. In adults with hyperkalaemia, there is no proof of added benefit of sodium zirconium cyclosilicate in comparison with the ACT.

Table 5 presents a summary of the results regarding the benefit assessment of sodium zirconium cyclosilicate in comparison with the ACT.

Table 5: Sodium zirconium cyclosilicate – probability and extent of added benefit

Indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with hyperkalaemia[b]	Individualized therapy upon the physician's discretion, taking into account aetiology, severity, and symptoms. Individualized therapy measures which represent the standard therapy of hyperkalaemia include treatment optimization for underlying diseases and comorbidities, particularly adaptation of drug therapy and, if necessary, a change in diet.[c]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. The G-BA assumes that patients in the present therapeutic indication do not suffer from potentially life-threatening hyperkalaemia which would require rescue therapy. Different therapeutic measures are available for rescue therapy.
c. According to the G-BA, any planned studies must provide for adaptation of standard therapy in the comparator arm.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The assessment described above departs from that by the company in that the company, rather than arriving at conclusions for the entire target population, drew separate conclusions for the 3 treatment situations it defined; it derived added benefit for patients requiring dialysis as well as for the correction phase, but not for the maintenance phase.

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.

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