Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL):

Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Sodium zirconium cyclosilicate hyperkalaemia)

of 16 September 2021

Contents

1. Legal basis 2

2. Key points of the resolution 2

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy 3

2.1.1 Approved therapeutic indication of sodium zirconium cyclosilicate (Lokelma) in accordance with the product information 3

2.1.2 Appropriate comparator therapy 3

2.1.3 Extent and probability of the additional benefit 5

2.1.4 Summary of the assessment 6

2.2 Number of patients or demarcation of patient groups eligible for treatment 6

2.3 Requirements for a quality-assured application 7

2.4 Treatment costs 7

3. Bureaucratic costs calculation 9

4. Process sequence 9

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes, in particular, the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical studies the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. Approved therapeutic indications,
2. Medical benefits,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Costs of therapy for the statutory health insurance,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the (German) market of the combination of active ingredient sodium zirconium cyclosilicate in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 April 2021. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 31 March 2021.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de), on 1 July 2021, thus initiating the written statement procedure. In addition, an oral hearing was also held.

The G-BA came to a resolution on whether an additional benefit of sodium zirconium cyclosilicate compared to the appropriate comparator therapy could be determined on the

basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of sodium zirconium cyclosilicate.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of sodium zirconium cyclosilicate (Lokelma) in accordance with the product information

Lokelma is indicated for the treatment of hyperkalaemia in adult patients

Therapeutic indication of the resolution (resolution from 16.09.2021):

See approved therapeutic indication.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with hyperkalaemia

Appropriate comparator therapy:

A patient-individual therapy taking into account the aetiology, severity and symptomatology.

Optimisation of the treatment of the underlying and concomitant diseases, particularly adjustment of the medicinal therapy and dietary changes, if necessary, are measures within the framework of patient-individual treatment, which represent the standard therapy in the treatment of hyperkalaemia.

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant benefit shall be preferred.
4. Comparative therapy should be part of the appropriate therapy in the therapeutic indication according to the generally accepted state of medical knowledge.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. Polystyrene sulfonates as calcium or sodium salts and the cation exchanger patiromer are approved in the indication area hyperkalaemia.

Since there are no indications for emergency treatment in the product information for sodium zirconium cyclosilicate and that normokalaemia is usually achieved within 24 to 48 hours according to the product information, it is assumed that the patients in the present therapeutic indication do not suffer from acutely life-threatening hyperkalaemia which therefore requires emergency treatment. Other medicinal and therapeutic measures are available for emergency treatment. Consequently, electrolyte solutions for haemodialysis, which are also approved in the context of existing hyperkalaemia, are not relevant for the present therapeutic indication.

on 2. The patient-individual therapy includes a change in diet as a non-medicinal treatment. In the present therapeutic indication, a low-potassium diet is generally indicated for all patients. This is also true for patients treated with sodium zirconium cyclosilicate.

For acute treatment, haemodialysis procedures can be considered for severe courses of hyperkalaemia. However, haemodialysis is not a standard treatment for hyperkalaemia. In addition, sodium zirconium cyclosilicateis not explicitly approved for the emergency treatment of life-threatening hyperkalaemia , so haemodialysis procedures cannot be considered an appropriate comparator therapy in the therapeutic indication of chronic therapy being assessed.

on 3. The following resolution of the G-BA is available for this therapeutic indication

- Resolution on the early benefit assessment of patiromer dated 10.09.2018

on 4. The general state of medical knowledge, on which the finding of the G-BA is based, was illustrated by systematic research for guidelines as well as reviews of clinical studies in the present therapeutic indication. There are only a few results from clinical studies with the highest degree of evidence for the treatment of hyperkalaemia.

The evaluation of the available evidence showed that patient-individual therapy is appropriate, taking into account the aetiology, severity and symptomatology. A patient-individual therapy defines the standard therapy in this context. In the present therapeutic situation, this means optimising the treatment of the underlying and concomitant diseases, in particular adjusting the medicinal therapy and, if necessary, changing the diet and treating the hyperkalaemia. In order to implement the

appropriate comparator therapy, a patient-individual adaptation of the standard therapy must therefore be ensured in the comparator arm of a study. This includes measures such as a change of diet, an adjustment of the dose and/or a change of the existing concomitant medication, and, if necessary, the direct treatment of the hyperkalaemia with polystyrene sulphonates. The marketing authorisation of the medicinal products must be taken into account.

Elements of patient-individual therapy may also be considered for patients treated with sodium zirconium cyclosilicate.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of sodium zirconium cyclosilicate is assessed as follows:

Adults with hyperkalaemia

An additional benefit is not proven.

Justification:

No relevant studies were identified for the evaluation of the additional benefit of sodium zirconium cyclosilicate for the treatment of adults with hyperkalaemia compared with the appropriate comparator therapy. Nevertheless, the pharmaceutical company submits the randomised controlled studies DIALIZE, ENERGISE, ZS-002, ZS-003 and D9482C00002 (ZS-002 Japan).

In all studies presented, sodium zirconium cyclosilicate was studied versus placebo. Patient-individual therapy, which, for example, enables the adjustment of medicinal therapy for underlying or concomitant diseases, was either not permitted in the studies presented, led to the discontinuation of study medication, or was only possible to a very limited extent, e.g. as emergency therapy. Thus, in the DIALIZE study, dialysate potassium concentration adjustment was allowed only during the first 4 weeks, if needed, in study participants requiring dialysis. In the ENERGIZE study, the administration of potassium-lowering medicinal products was permitted only as emergency therapy. In the ZS-002 study, dietary changes were explicitly not planned. In the ZS-003 study, all concomitant medications were to be continued constantly during the study, while the use of emergency therapies led to the discontinuation of study medication. In the ZS-002 Japan study, medicinal products beyond the study medication were not allowed for the treatment of hyperkalaemia. Overall, it can be concluded that patient-individual therapy was not guaranteed in the comparator arm of the studies presented, in particular due to the non-permitted or only limited permitted adjustment of medicinal therapy, and that the appropriate comparator therapy was therefore not implemented.

In addition, the duration of the studies submitted by the pharmaceutical company, which for example amounted to a maximum of 10 weeks in the DIALIZE study, 8 days in the ENERGIZE study or 3 weeks in the ZS-003 study, is not sufficient for the assessment of the additional benefit in the therapeutic indication of hyperkalaemia. This is because a minimum duration of 24 weeks is considered necessary for the early benefit assessment for chronic diseases.

Consequently, the duration of the studies presented is clearly too short to derive an additional benefit.

Furthermore, the subdivision into different therapy situations based on the dosage recommendations of the product information (correction phase, maintenance phase and dialysis requirement) carried out by the pharmaceutical company is viewed critically. The fact that different dosages are recommended according to the product information does not justify a subdivision of the patient population. In particular, it is not appropriate to assess the correction and maintenance phases separately. The therapy concept of hyperkalaemia instead comprises both phases (correction and maintenance phase). In addition, patients requiring dialysis are already covered by the approved therapeutic indication for the treatment of hyperkalaemia. A subdivision into different therapy situations is therefore not appropriate.

In summary, the studies presented by the pharmaceutical company are not suitable for evaluating a comparison of sodium zirconium cyclosilicate versus the appropriate comparator therapy. The treatment administered in the comparator arm of the studies does not correspond to the appropriate comparator therapy. Secondly, the study duration of a maximum of 10 weeks in the DIALIZE study is clearly too short for an assessment of the additional benefit. An additional benefit is not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Lokelma with the active ingredient sodium zirconium cyclosilicate.

Sodium zirconium cyclosilicate is approved for the treatment of hyperkalaemia in adult patients.

In the therapeutic indication to be considered, the following patient groups were defined:

Adults with hyperkalaemia.

The G-BA determined the appropriate comparator therapy for the above patient group as:

> A patient-individual therapy taking into account the aetiology, severity and symptomatology.
>
> Optimisation of the treatment of the underlying and concomitant diseases, particularly adjustment of the medicinal therapy and dietary changes, if necessary, are measures within the framework of patient-individual treatment, which represent the standard therapy in the treatment of hyperkalaemia.

No relevant studies compared to the appropriate comparator therapy were identified. Also, in the studies submitted by the pharmaceutical company for a comparison of sodium zirconium cyclosilicate versus placebo, the appropriate comparator therapy was not implemented, as a patient-individual therapy, for example by adjustments of the medicinal therapy, was largely not possible or led to the discontinuation of the study medication. Furthermore, the selected study duration in the studies is too short for an assessment of the additional benefit. An additional benefit is not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

Overall, the information provided by the pharmaceutical company is subject to uncertainties. In order to give due consideration to these uncertainties, during the determination of the patient numbers,[2] both the data of a routine data analysis submitted by the pharmaceutical company and the underlying data in the previous resolution[3] regarding the therapeutic indication of hyperkalaemia are taken into consideration.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Lokelma (active ingredient: sodium zirconium cyclosilicate) at the following publicly accessible link (last access: 10 August 2021):

https://www.ema.europa.eu/en/documents/product-information/lokelma-epar-product-information_en.pdf

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 August 2021).

For the presentation of the costs, one year is assumed for all medicinal products.

Costs of the medicinal products:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. The required number of packs of a particular potency was first determined based on consumption to calculate the annual treatment costs. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

Medicinal product to be assessed: Sodium zirconium cyclosilicate

Since the total population includes patients with and without dialysis requirements, the presentation of annual treatment costs takes into account both dialysis-requiring and non-dialysis-requiring dosages in each case in the context of long-term therapy. The lower limit for non-dialysis dosing is 5 g every other day, and the upper limit is 10 g daily. In the context of dialysis, it is assumed that there are 2 to 4 dialysis days per week and therefore 3 to 5 non-dialysis days per week. Since sodium zirconium cyclosilicate cannot be administered on dialysis days, 3 to 5 treatment days with sodium zirconium cyclosilicate per week are assumed. This results in a dialysis-requiring dosage of 15 g (10 g + 5 g sachets) 5 times every 7 days for the upper limit and 5 g 3 times every 7 days for the lower limit. The annual treatment costs for patients not requiring dialysis are within the cost range of patients requiring dialysis.

[2] See IQWiG dossier assessment (A20-40)
[3] https://www.g-ba.de/downloads/39-261-3480/2018-09-20_AM-RL-XII_Patiromer_D-351_BAnz.pdf

The costs of a possibly necessary titration phase have not been presented since the therapy for hyperkalaemia is a continuous long-term therapy, and the titration is patient-individual.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
without dialysis requirement				
Sodium zirconium cyclosilicate	Continuously, 1 x every 2 days – 1 x daily	182.5 – 365	1	182.5 – 365
with dialysis requirement				
Sodium zirconium cyclosilicate	3 - 5 x in 7 days	52.1	3 - 5	156.3 – 260.5
Appropriate comparator therapy				
Patient-individual therapy	Patient-individual			

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
without dialysis requirement					
Sodium zirconium cyclosilicate	5 g - 10 g	5 g - 10 g	1 x 5 g – 1 x 10 g	182.5 - 365	182.5 x 5 g – 365 x 10 g
with dialysis requirement					
Sodium zirconium cyclosilicate	5 g – 15 g	15 g – 75 g	1 x 5 g – 1 x (1 x 5 g + 1 x 10 g)	156.3 – 260.5	156.3 x 5 g – (260.5 x 5 g + 260.5 x 10 g)
Appropriate comparator therapy					
Patient-individual therapy	Patient-individual				

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Sodium zirconium cyclosilicate 5g	30 POS	€ 390.33	€ 1.77	€ 21.00	€ 367.56
Sodium zirconium cyclosilicate 10g	30 POS	€ 390.33	€ 1.77	€ 21.00	€ 367.56
Appropriate comparator therapy					
Patient-individual therapy	Patient-individual				
Abbreviations: POS = Powder for oral suspension					

LAUER-TAXE® last revised: 15 August 2021

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be considered as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 26 July 2016, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 31 March 2021, the pharmaceutical company submitted a dossier for the benefit assessment of sodium zirconium cyclosilicate to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 1 April 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient sodium zirconium cyclosilicate.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 June 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 July 2021. The deadline for submitting written statements was 22 July 2021.

The oral hearing was held on 10 August 2021.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and the representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 7 September 2021, and the proposed resolution was approved.

At its session on 16 September 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Sub-committee Medicinal product	26 July 2016	Determination of the appropriate comparator therapy
Working group Section 35a	4 August 2021	Information on statements received; preparation of the oral hearing
Sub-committee Medicinal product	10 August 2021	Conduct of the oral hearing
Working group Section 35a	17 August 2021 31 August 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Sub-committee Medicinal product	7 September 2021	Final discussion of the draft resolution
Plenum	16 September 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 September 2021

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken