Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Berotralstat (hereditary angioedema)

of 2 December 2021

Contents

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. treatment costs for statutory health insurance funds,
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 active ingredient berotralstat in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 June 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 4 June 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 15 September 2021, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of berotralstat 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, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has assessed 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 berotralstat.

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 berotralstat (Orladeyo) in accordance with the product information

Orladeyo is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.

Therapeutic indication of the resolution (resolution from 2 December 2021):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

<u>Adolescent and adult patients aged 12 years and older with recurrent attacks of hereditary angioedema</u>

Appropriate comparator therapy for berotralstat for routine prevention:

routine prevention with C1 esterase inhibitor

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

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to 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.

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

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 as 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: According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

on 1. In addition to berotralstat, the active ingredients C1 esterase inhibitor, the antifibrinolytic tranexamic acid and the plasma kallikrein inhibitor lanadelumab are approved in the present therapeutic indication.

on 2. For the treatment of hereditary angiooedema, no non-medical measures can be considered as the appropriate comparator therapy.

on 3. In the present therapeutic indication, there is a resolution on lanadelumab due to a reassessment after the turnover threshold of € 50 million was exceeded on 4 November 2021.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

It is assumed that the therapeutic indication of berotralstat only includes patients with type I or type II HAE (hereditary angiooedema), who are characterised by a deficiency or a defect of the C1 esterase inhibitor. The goal of treatment for affected patients is to reduce the resulting angioedema or HAE attacks.

If acute treatment of HAE attacks alone is no longer sufficient, the guidelines recommend long-term prevention with C1 esterase inhibitor. This therapy can reduce the number, duration and severity of HAE attacks. According to current guidelines, treatment with antifibrinolytics is a secondary therapy option. For the active ingredient lanadelumab, the additional benefit compared to the appropriate comparator therapy is considered not proven by the resolution of 4 November 2021. In addition, it is not eligible as an appropriate comparator therapy due to insufficient market availability. Thus, long-term prevention with C1 esterase inhibitor was determined as the appropriate comparator therapy with berotralstat for long-term prevention in patients aged 12 years and older with hereditary angioedema.

In addition to appropriate long-term prevention, acute treatment of HAE attacks should generally also be possible where necessary. It is pointed out here that the possibility of

acute treatment of HAE attacks should also exist in both study arms. In order to increase the interpretability of the results, it is also recommended to document the concomitant medication or the medication for the acute treatment of HAE attacks with dosage and duration during the study and to present it in the dossier.

The marketing authorisation and dosage specifications in the product information of the active ingredients must be considered; deviations must be justified separately.

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 berotralstat is assessed as follows:

For adolescents and adults aged 12 years and older with recurrent attacks of hereditary angioedema, an additional benefit of berotralstat compared with the appropriate comparator therapy has not been proven.

Justification:

No comparative data versus the appropriate comparator therapy were presented for the assessment of the additional benefit of berotralstat for the long-term prevention of recurrent attacks of hereditary angioedema in adolescents and adults aged 12 years and older. Thus, the additional benefit is not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Orladeyo with the active ingredient berotralstat.

Berotralstat is approved in adolescents and adults aged 12 years and older for the long-term prevention of recurrent attacks of hereditary angioedema.

Routine prevention with C1 esterase inhibitor was determined to be the appropriate comparator therapy.

No comparative data versus the appropriate comparator therapy were presented. Thus, 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. The resolution is based on the figures from the resolution on lanadelumab of 4 November 2021 in the same therapeutic indication. However, these figures are subject to the following uncertainties:

The calculation of the lower limit of the number of patients with HAE in Germany is based on an estimated HAE prevalence rate for Greece (which is low compared to other countries), as no data are available for Germany according to the pharmaceutical company. The extent to which the data can be transferred to the German health care context is therefore questionable. Further uncertainties arise for the upper limit of patients with HAE in Germany, which is based on an expert survey. The number of patients determined was limited to the percentage of patients who were being treated with long-term prevention at the time of the survey. It can be assumed that the number of patients may be underestimated as this excluded patients who did not receive long-term prevention but are eligible for routine prevention. The expert survey was conducted in 2018. However, the number of patients eligible for routine prevention in the current year may be higher.

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 Orladeyo (active ingredient: berotralstat) at the following publicly accessible link (last access: 16 November 2021):

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

Treatment with berotralstat should only be initiated and monitored by doctors experienced in treating adolescent and adult patients with hereditary angiooedema.

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 November 2021).
For the cost representation, only the dosages of the general case are considered. If the treatment duration is not limited, initial induction schemes are not considered for the cost representation. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

According to the product information, the recommended dose of the medicinal product to be assessed, berotralstat, is 150 mg once daily for adults and adolescents aged 12 years and older and weighing ≥ 40 kg.

Medicinal products with different dosage specifications and modes of administration (IV and SC) are available for the appropriate comparator therapy of C1 esterase inhibitors. The most economical dosage form is taken into account for the cost calculation.

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Berotralstat	continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
C1 esterase inhibitor	continuously, every 3 - 4 days	91.3 – 121.7	1	91.3 – 121.7

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Usage by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Berotralstat	150 mg	150 mg	1 x 150 mg	365	365 x 150 mg
Appropriate comparator therapy					
C1 esterase inhibitor	1,000 I.U.	1,000 I.U.	2 x 500 I.U.	91.3 – 121.7	182.6 x 500 I.U. - 243.4 x 500 I.U.

Costs:

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 Section 130 and Section 130 a SGB V. 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 on the basis of the costs per pack after deduction of the statutory rebates.

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					
Berotralstat	98 HC	€ 65,876.83	€ 1.77	€ 3,758.96	€ 62,116.10
Appropriate comparator therapy					
C1 esterase inhibitor 500 I.U.	2 PSI	€ 1,861.43	€ 1.77	€ 103.03	€ 1,756.63
Abbreviations: HC = hard capsules, PSS = Powder and solvent for solution for injection					

LAUER-TAXE® last revised: 15 November 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 taken into account 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 assessed 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 23 January 2018, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 4 June 2021, the pharmaceutical company submitted a dossier for the benefit assessment of berotralstat to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 8 June 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 berotralstat.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 September 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 15 September 2021. The deadline for submitting written statements was 6 October 2021.

The oral hearing was held on 25 October 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 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 were discussed at the session of the subcommittee on 23 November 2021, and the proposed resolution was approved.

At its session on 2 December 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	23 January 2018	Determination of the appropriate comparator therapy
Working group Section 35a	19 October 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	25 October 2021	Conduct of the oral hearing
Working group Section 35a	2 November 2021 16 November 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	23 November 2021	Concluding discussion of the draft resolution
Plenum	2 December 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 2 December 2021

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

Prof. Hecken