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 Lanadelumab (reassessment of an orphan drug after exceeding the EUR 50 million turnover limit (hereditary angioedema, prevention, ≥ 12 years))

of 4 November 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 or 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 of the combination of active ingredient lanadelumab on the (German) market 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 February 2019. 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 6 VerfO on 10 May 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 16 August 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 lanadelumab 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 lanadelumab.

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 for lanadelumab (according to marketing authorisation of 22 November 2018)

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

Therapeutic indication of the resolution (resolution of 04.11.2021):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adolescents and adults 12 years of age and older with recurrent attacks of hereditary angioedema

Appropriate comparator therapy of lanadelumab for routine prevention:

A routine prevention with C1 esterase inhibitor

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.

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 as a comparator therapy, this must be available within the framework of the SHI system.

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

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 the present therapeutic indication, the active ingredients C1-esterase inhibitor, the antifibrinolytic tranexamic acid and the plasma kallikrein inhibitor berotralstat are approved as long-term prevention of hereditary angioedema in addition to the active ingredient to be assessed.

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

on 3. There are no other relevant resolutions in the present therapeutic indication.

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 lanadelumab only includes patients with HAEs type I or type II, which 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 lower-ranking therapeutic option, so that long-term prevention with C1 esterase inhibitor was determined as the appropriate comparator therapy for lanadelumab as long-term prevention for patients over 12 years of age with hereditary angioedema.

Acute treatment of HAE attacks should generally - if necessary - also be possible in addition to appropriate long-term prevention. It is noted 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 present it in the dossier.

The marketing authorisations and dosage information in the product information of the active ingredient are to be observed; deviations are to be justified separately.

The benefit assessment procedure for the active ingredient berotralstat, which was approved in March 2021, began in May 2021. Therefore, and due to the fact that they are not yet available on the market for a long time, the active ingredient cannot be considered as an appropriate comparator therapy for the present procedure.

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 lanadelumab is assessed as follows:

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

Justification:

In its dossier for the assessment of the additional benefit of lanadelumab, the pharmaceutical company does not present any directly comparative studies regarding the appropriate comparative therapy, but the non-randomised PATCH study and additionally two non-randomised before-after comparisons.

PATCH study

The PATCH study is a retrospective comparison of individual patient data from three studies under adjustment for confounders with data from the placebo-controlled RCT HELP and the single-arm extension study HELP-OLE and, for the comparator therapy, data from the single-arm extension study CHANGE-3 (C1 esterase inhibitor). Another study identified as relevant (COMPACT-OLE) was not used by the pharmaceutical company because there was no access to the individual patient data.

In the PATCH study, the included patient populations have a pronounced structural inequality with regard to the confounders surveyed, which is not sufficiently compensated for by confounder adjustment. Moreover, the information available in the dataset on the confounders identified as relevant is incomplete. The dossier does not sufficiently explain how a lack of adjustment for potentially relevant confounders affects the effect estimate of individual endpoints.

Due to this limitation, the PATCH study is not suitable for assessing the additional benefit of lanadelumab compared with the appropriate comparator therapy.

Before-after comparisons

The prospective observational study of Hahn 2020 and a retrospective post hoc evaluation of the placebo-controlled RCT HELP, which included patients who had already received routine prevention with C1 esterase inhibitor before the start of the study, were presented as before-after comparisons.

In the Hahn 2020 study, after 6 months of therapy with lanadelumab, the monthly number of HAE attacks and health-related quality of life were compared with the period of the last 6 months before the time of enrolment.

In the RCT HELP, the monthly number of HAE attacks under lanadelumab during the randomised treatment phase was compared with the previous number of HAE attacks under C1 esterase inhibitor outside the study documented at the time of enrolment. This leads to

the fact that before-after comparison of the treatment situations in the post hoc evaluation of the RCT HELP is not sufficient since the comparative therapy took place under uncontrolled conditions, while the treatment with lanadelumab under controlled study conditions.

In addition, no endpoints in the category side effects were reported in either comparison. Due to these limitations, the before-after comparisons are not suitable for assessing the additional benefit of lanadelumab compared with the appropriate comparator therapy.

Overall assessment / conclusion

Overall, on the basis of the studies presented, no conclusions can be drawn regarding the additional benefit of lanadelumab compared with the appropriate comparator therapy. An additional benefit is not proven.

2.1.4 Summary of the assessment

The present evaluation is a new benefit assessment of the active ingredient lanadelumab due to the exceeding of the €50 million turnover limit. Takhzyro (active ingredient lanadelumab) was approved as an orphan drug and is indicated for the treatment of adolescents and adults aged 12 years and older for the routine prevention of recurrent attacks of hereditary angioedema (HAE).

The G-BA determined routine prevention with C1 esterase inhibitor as an appropriate comparator therapy.

For this therapeutic indication, the pharmaceutical company presents the non-randomised PATCH study and two non-randomised before-after comparisons.

The PATCH study is a retrospective comparison of individual patient data from three studies (RCT HELP, single-arm extension study HELP-OLE, single-arm extension study CHANGE-3). However, due to a pronounced structural inequality of the patient population, which is not adequately compensated for by confounder adjustment, the PATCH study is not suitable for deriving an additional benefit of lanadelumab compared to the appropriate comparator therapy.

The before-after comparisons are also not suitable for the assessment of the additional benefit due to various limitations.

Overall, no conclusions can be drawn regarding the additional benefit of lanadelumab based on the data presented. Therefore, an additional benefit of lanadelumab compared to the appropriate comparator therapy 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 information is based on data provided by the pharmaceutical company in the dossier. However, the information is subject to 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. Therefore, the extent to which the data can be transferred to the German healthcare context is 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. Since this excluded patients who did not receive long-term prevention but are eligible for routine prevention, it can be assumed that the number of patients may be underestimated. 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 Takhzyro (active ingredient: lanadelumab) at the following publicly accessible link (last access: 13 October 2021):
https://www.ema.europa.eu/en/documents/product-information/takhzyro-epar-product-information_en.pdf

Treatment with lanadelumab should only be initiated and monitored by doctors experienced in treating adolescent and adult patients with hereditary angioedema (HAE).

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 October 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 lanadelumab is 300 mg every 2 weeks. A dose reduction of 300 mg lanadelumab every 4 weeks may be considered in treated patients free of attacks, especially in patients with low body weight.

For the appropriate comparator therapy of C1-esterase inhibitors, medicinal products with different dosage information and administration routes (IV and SC) are available. For the cost calculation, the most economical dosage form is taken into account.

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 or 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 or patient//year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Lanadelumab	Continuously, every 14 – every 28 days	13.0 -26.1	1	13.0 -26.1
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/ or patient/ treatment days	Usage by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Lanadelumab	300 mg	300 mg	1 x 300 mg	13.0 – 26.1	13.0 - 26.1 x 300 mg
Appropriate comparator therapy					
C1 esterase inhibitor	1000 I.U.	1000 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 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. 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.

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					
Lanadelumab 300 mg	6 IFE	€ 93,862.48	€ 1.77	€ 5,357.23	€ 88,503.48
Appropriate comparator therapy					
C1 esterase inhibitor 500 I.U.	2 PSS	€ 1,861.43	€ 1.77	€ 103.03	€ 1,756.63
Abbreviations: PSS = Powder and solvent for solution for injection, IFE = solution for injection in a pre-filled syringe					

LAUER-TAXE® last revised: 15 October 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 the 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 23 January 2018, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 10 May 2021, the pharmaceutical company submitted a dossier for the benefit assessment of lanadelumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 6 VerfO.

By letter dated 11 May 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 lanadelumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 12 August 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 16 August 2021. The deadline for submitting written statements was 6 September 2021.

The oral hearing was held on 27 September 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 was discussed at the session of the subcommittee on 26 October 2021, and the proposed resolution was approved.

At its session on 4 November 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	14 September 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	27 September 2021	Conduct of the oral hearing
Working group Section 35a	5 October 2021 19 October 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	26 October 2021	Concluding discussion of the draft resolution
Plenum	4 November 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 4 November 2021

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

Prof. Hecken