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)

Brolucizumab (reassessment after the deadline (neovascular age-related macular degeneration))

of 2 May 2024

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 trials 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 benefit,
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 the 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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The pharmaceutical company submitted a dossier on 9 March 2020 for the early benefit assessment of the active ingredient brolucizumab (Beovu) to be assessed. For the resolution of 3 September 2020 made by the G-BA in this procedure, a limitation up to 1 November 2023 was pronounced.

In accordance with Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Beovu recommences when the deadline has expired.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 5 VerfO on 18 October 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 1 February 2024 on the G-BA website (www.g-ba.de), 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 brolucizumab compared with 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, as well of the addendum drawn up by the IQWiG on the benefit assessment. 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 brolucizumab.

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 Brolucizumab (Beovu) in accordance with the product information

Beovu is indicated in adults for the treatment of:

- neovascular (wet) age-related macular degeneration (AMD)
- visual impairment due to diabetic macular oedema (DME).

Therapeutic indication of the resolution (resolution of 2 May 2024):

Beovu is indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (AMD).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with neovascular (wet) age-related macular degeneration (AMD)

Appropriate comparator therapy for brolucizumab:

– Aflibercept or faricimab or ranibizumab

1 General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA 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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

on 1. In addition to the marketing authorisation for brolucizumab, there are also marketing authorisations for aflibercept, faricimab and ranibizumab in the present therapeutic indication. The active ingredient verteporfin is approved for the "treatment of adults with exudative (wet) age-related macular degeneration (AMD) with predominantly classic subfoveal choroidal neovascularisation". Pegaptanib is no longer approved in the EU.

on 2. The following non-medicinal treatment options are available in the present therapeutic indication: Photodynamic therapy (PDT), photocoagulation by laser, proton therapy for age-related macular degeneration (resolution of 17 September 2009) and photodynamic therapy (PDT) with verteporfin for age-related wet macular degeneration with subfoveolar classic choriodal neovascularisation (resolution of 16 October 2000).

on 3. The following resolutions of the G-BA on the benefit assessment according to Section 35a SGB V are available for the present therapeutic indication:

- Aflibercept (resolution of 6 June 2013)
- Brolucizumab (resolution of 3 September 2020)
- Faricimab (resolution of 6 April 2023)

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic 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".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

Based on the aggregated evidence, it can be stated that according to the guideline recommendations, the standard therapy for the targeted treatment setting consists of treatment with a vascular endothelial growth factor (VEGF) inhibitor, without a clear superiority of a specific inhibitor available in Germany being shown. This applies both to initial therapy in therapy naive patients and to a switch after an inadequate response to a VEGF inhibitor. Aflibercept, brolucizumab, faricimab and ranibizumab are approved in the relevant therapeutic indication.

In this therapeutic indication, resolutions on the benefit assessment according to Section 35a SGB V have been made for the active ingredients aflibercept, brolucizumab and faricimab. An additional benefit compared to the appropriate comparator therapy has not been proven for any of the active ingredients mentioned.

Against the background of the aggregated evidence in the indication the significance of non-medicinal interventions is considered lower than the VEGF inhibitors established in neovascular (wet) AMD.

On the basis of the available, aggregated evidence and on the basis of the authorisation status and taking into account the statements made by the clinical experts during the oral hearing, the G-BA determines aflibercept or faricimab or ranibizumab as the appropriate comparator therapy for brolucizumab for the treatment of adults with neovascular (wet) AMD. The active ingredients of the specific appropriate comparator therapy are suitable both for patients who are receiving treatment for their neovascular (wet) AMD for the first time and in the sense of a switch for patients previously treated with VEGF inhibitors after an inadequate response to the existing anti-VEGF therapy.

The appropriate comparator therapy determined here includes several therapy options. These therapeutic alternatives are equally appropriate for the comparator therapy.

Change of the appropriate comparator therapy

To date, the VEGF inhibitors aflibercept or ranibizumab have been considered appropriate comparator therapies for adults with neovascular (wet) age-related macular degeneration (AMD). In the opinion of the clinicians involved in the written statement procedure, this no longer corresponds to the current medical treatment situation. According to this study, faricimab has a significance comparable to aflibercept and ranibizumab in the treatment of nAMD. The options mentioned are to be regarded as equivalent; a differential therapy recommendation or criteria for the selection of one of these treatment options are not available. Thus, aflibercept, ranibizumab and faricimab should be considered equally appropriate therapy options in the overall assessment.

For this reason, the G-BA considers it appropriate to change the appropriate comparator therapy and to determine a therapy with aflibercept or faricimab or ranibizumab as the appropriate comparator therapy.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of brolucizumab is assessed as follows:

An additional benefit is not proven.

Justification:

For the assessment of the additional benefit, the pharmaceutical company presents the data of the double-blind, randomised, active-controlled TALON study (CRTH258A2303).

The RCT TALON, which compares brolucizumab with aflibercept in adults (≥ 50 years) with neovascular (wet), age-related macular degeneration who have not yet received therapy directed against vascular endothelial growth factor (VEGF) over a treatment period of 64

weeks, was completed on 09.09.2022. A total of 734 patients were enrolled and randomised to 64-week treatment with either 6 mg brolucizumab (N = 366) or 2 mg aflibercept (N = 368).

Therapy initiation with brolucizumab and aflibercept was carried out with 3 consecutive injections at intervals of 4 weeks. In an amendment to the product information for brolucizumab made after the start of study, an additional, alternative treatment regimen for build-up dosing was introduced, which was therefore not possible in the TALON study. After initiation, both active ingredients were followed by a further injection after 8 weeks with subsequent so-called treat-to-control treatment from week 16. The treat-to-control treatment phase allowed patient-individual adaptation of the treatment intervals depending on the disease activity.

According to the first version of the study protocol, the minimum dosing interval of brolucizumab and aflibercept in the maintenance phase was allowed to be 4 weeks. Due to a safety measure, the study protocol of the TALON study and the product information for brolucizumab were amended to the effect that the minimum dosing interval in the maintenance phase must be at least 8 weeks.

The change in the study protocol of the TALON study affected both treatment arms, although aflibercept may continue to be administered in a 4-week dosing interval in the maintenance phase according to the current product information.

On the use of aflibercept in accordance with the product information:

According to the study report, 22.5% of patients in the aflibercept arm had to discontinue study treatment at week 64 and 17.9% at week 32 due to the protocol amendment, although they could have continued treatment in the maintenance phase with a 4-week dosing interval according to the current product information for aflibercept. Conversely, it is assumed that the patients remaining in the study were adequately treated at their respective dosing interval (≥ 8 weeks). Since less than 80% of patients in the aflibercept arm were treated in accordance with the product information at week 64, this assessment is not based on the data for week 64, but instead on the data for week 32.

On the use of brolucizumab in accordance with the product information:

In the brolucizumab arm, it can be assumed that by week 32, a total of 22% of patients were treated at least once at a dosing interval of < 8 weeks that did not comply with the product information. The data subsequently submitted by the pharmaceutical company after the oral hearing show that a total of 11% of patients in the brolucizumab arm were treated only once at a dosing interval of less than 8 weeks. This also includes deviations of only a few days from the dosing interval conforming to the product information, even if it is not possible to deduce from the information provided by the pharmaceutical company how many patients this affects.

With regard to the lack of consideration of alternative build-up dosing in the TALON study, the G-BA assumes that both build-up dosage regimens are equivalent in the absence of specific criteria according to which one of the two possible dosage regimens is to be preferred for the patients to be treated or selected on a patient-individual basis. Against this background, the offer of one of the two alternative dosage regimens represents an appropriate use in line with the product information.

Overall, a one-time shortfall of a dosing interval of 8 weeks in the maintenance phase and, in particular, deviations of only a few days are considered to be a sufficient approximation to the use of brolucizumab in accordance with the product information, so that the results of the TALON study at week 32 are used for the present benefit assessment. However, due to the percentage of patients with dosing intervals that do not comply with the product information, the results of the TALON study are subject to uncertainties, which are taken into account in the interpretation of the results.

Extent and probability of the additional benefit

Mortality

For the endpoint of overall mortality, there was a statistically significant difference to the disadvantage of brolucizumab in the TALON study.

Morbidity

Best Corrected Visual Acuity (BCVA) - improvement by ≥ 10 as well as ≥ ≥ 15 ETDRS-letters

BCVA was measured in both studies using ETDRS eye charts. The eye chart consists of 14 lines of optotypes, each with 5 letters, and is thus made up of a total of 70 letters. The size of the letters decreases with each line. The BCVA results from the number of correctly read letters plus 30 at a distance of 4 metres and directly from the number of correctly read letters at a distance of 1 metre. BCVA can take values between 0 and 100, with higher values indicating better visual acuity.

In the present indication, a change in visual acuity is considered patient-relevant. With the dossier the pharmaceutical company submitted evaluations of both the improvement and the deterioration of BCVA. For the present benefit assessment, the responder analyses for improvement or deterioration by ≥ 10 ETDRS-letters (corresponding to 2 lines) or for improvement by ≥ 15 ETDRS-letters (corresponding to 3 lines) are used.

There was no statistically significant difference between the treatment groups for the endpoint of best corrected visual acuity (responder analysis for improvement or deterioration by ≥ 10 ETDRS-letters and ≥ 15 ETDRS-letters).

Health status (National Eye Institute Visual Function Questionnaire-25 [NEI VFQ-25], general health status subscale)

The NEI VFQ-25 questionnaire is designed to measure visual acuity-related quality of life and consists of a total of 26 items and 12 subscales, of which 25 items (11 subscales) relate to vision and 1 item (1 subscale) addresses general health. The subscale on general health is assigned to the morbidity category.

The pharmaceutical company submits responder analyses carried out post hoc for the general health status subscale for improvement by 15 points in each case. Responder analyses on deterioration are not presented, although a deterioration would be equally relevant in the present therapeutic indication.

For the endpoint of health status (collected using NEI VFQ-25, general health status subscale), there was no statistically significant difference between the treatment groups.

Quality of life

NEI VFQ-25 (sum score)

The NEI VFQ-25 is a questionnaire for measuring visual acuity-related quality of life, consisting of a total of 26 items and 12 subscales. Of these, 25 items (11 subscales) ask about vision and 1 item (1 subscale) about general health.

The values of all items are transformed to a score from 0 to 100 and a score averaged over the items of the subscale is calculated for each subscale. The sum score finally results from the mean of the averaged scores of the subscales. The general health subscale is not included here. The sum score of the NEI VFQ-25 can take values between 0 and 100, with higher values indicating a better visual acuity-related quality of life.

For the endpoint of health-related quality of life, the pharmaceutical company submits responder analyses conducted post hoc to improve the sum score of the NEI VFQ-25 and the 12 subscales by ≥ 15 points as well as continuous evaluations. Since the pharmaceutical company did not submit any responder analyses on the deterioration of the NEI VFQ-25 by ≥ 15 points, the continuous evaluations are used here.

For the endpoint of health-related quality of life (collected using sum score of the NEI VFQ-25), there was no statistically significant difference between the treatment groups.

Side effects

SAEs

For the endpoint of SAEs, no statistically significant difference was detected between the treatment groups.

Discontinuation due to AEs

For the endpoint of discontinuation due to AEs, there was a statistically significant difference to the disadvantage of brolucizumab.

(Serious) intraocular inflammation (including endophthalmitis and retinal vascular occlusion)

In the study report, the pharmaceutical company defines ocular AESI as events from the categories of endophthalmitis, intraocular inflammation and retinal vascular occlusion. The ocular AESI are therefore used as a suitable operationalisation for the endpoint of intraocular inflammation for the present benefit assessment. Since the overall rate of ocular SAEs largely includes events that also correspond to an ocular AESI, the ocular SAEs are used as a suitable operationalisation for serious intraocular inflammation for the present benefit assessments.

There was a statistically significant difference to the disadvantage of brolucizumab for the endpoint of intraocular inflammation. For the serious intraocular inflammation, there was no statistically significant difference between the treatment groups.

Overall assessment

For the assessment of the additional benefit of brolucizumab, the evaluation of the double-blind, randomised, active-controlled phase III TALON study versus aflibercept is available at week 32.

In summary, there was a statistically significant disadvantage of brolucizumab compared to aflibercept in the endpoint category of mortality at week 32. However, against the background

of the overall low number of events (a total of 4 deaths in the intervention arm: 2 patients died from cardiac disorders and 2 in connection with COVID-19) and the heterogeneity of the causes, it is unclear to what extent there is a causal relationship between the treatment in the study and the deaths that occurred. For this reason, the effect shown in mortality is not included in the overall assessment to derive an additional benefit.

There was no statistically significant difference between brolucizumab and aflibercept at week 32 in the endpoint categories of morbidity, shown using the best corrected visual acuity and the general health status subscale of the NEI VFQ-25, as well as quality of life, determined using the sum score of the NEI VFQ-25.

In the endpoint category of side effects, the overall rate of the SAEs did not show any statistically significant difference between the treatment arms. On the contrary, there was a statistically significant disadvantage of brolucizumab compared to aflibercept for the endpoint of discontinuation due to AEs. In detail, there was also a statistically significant disadvantage of brolucizumab for the endpoint of intraocular inflammation, but not for the endpoint of severe intraocular inflammation.

Taking into account the overall low discontinuation rates of < 5% in both study arms and the fact that the events that led to therapy discontinuation were predominantly not serious, the negative effects in the endpoint category of side effects are not adequate to justify the conclusion of a lower benefit of brolucizumab compared to aflibercept.

In the overall assessment, an additional benefit of brolucizumab for adults with nAMD compared to the appropriate comparator therapy aflibercept is not proven.

2.1.4 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient brolucizumab due to the expiry of the limitation of the resolution of 3 September 2020.

The therapeutic indication assessed here is as follows:

Beovu is indicated in adults for the treatment of neovascular (wet) age-related macular degeneration (AMD).

The G-BA determined the active ingredients aflibercept, faricimab and ranibizumab as the appropriate comparator therapy.

For the assessment of the additional benefit, the pharmaceutical company presents the data of the TALON RCT at week 32, which compared brolucizumab to aflibercept.

The TALON study showed a statistically significant disadvantage of brolucizumab in terms of mortality. Since a causal relationship between the treatment in the study and the deaths that occurred is questionable, this does not result in a relevant disadvantage for the benefit assessment.

There were no statistically significant differences between brolucizumab and aflibercept in the endpoint categories of morbidity and quality of life.

In the endpoint category of side effects, the overall rate of the SAEs did not show any statistically significant difference between the treatment arms. In the endpoint of discontinuation due to AEs, however, there was a statistically significant disadvantage of

brolucizumab compared to aflibercept. In addition, there was a statistically significant disadvantage of brolucizumab in the endpoint of intraocular inflammation.

Taking into account the overall low discontinuation rates of < 5% in both study arms and the fact that the events that led to therapy discontinuation were predominantly not serious, the negative effects in the endpoint category of side effects are not adequate to justify the conclusion of a lower benefit of brolucizumab compared to aflibercept.

In the overall assessment, an additional benefit of brolucizumab for adults with nAMD compared to the appropriate comparator therapy aflibercept 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).

The resolution is based on the information from the dossier assessment of the IQWiG (mandate A23-101). These are based on the information provided by the pharmaceutical company in the dossier and are identical to the figures from the dossier for the initial benefit assessment of brolucizumab.

The derivation of the patient numbers in the dossier for the active ingredient brolucizumab is basically comprehensible and lies in a plausible order of magnitude. Due to the uncertain data basis for the estimation of the SHI target population, the specification of a range is fundamentally appropriate despite methodological weaknesses and thus takes this uncertainty into account.

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 Beovu (active ingredient: brolucizumab) at the following publicly accessible link (last access: 7 March 2024):

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

Treatment with brolucizumab may only be initiated and monitored by doctors experienced in the therapy of neovascular (wet) age-related macular degeneration.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for patients.

In particular, the training material contains information and warnings about infective endophthalmitis and intraocular inflammation.

If the visual and morphological parameters indicate that the patient will not benefit from further treatment, treatment with brolucizumab should be discontinued.

Brolucizumab has a Dear Healthcare Professional Communication ("Rote-Hand-Brief") from November 2021 to reduce the known risk of intraocular inflammation including retinal vasculitis and/or retinal vascular occlusion.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 April 2024).

In the present case, the treatment duration, consumption and costs shown refer to the first year of treatment on the one hand and to the subsequent years on the other; whole injection solutions consumed within the first year were rounded up for the first year of treatment.

Due to the possible patient-individual approach regarding the adjustment of the treatment intervals according to the product information, the possible upper and lower limits of the costs are presented in the present resolution for the following years.

Patient-individual dose adjustments, e.g. because of side effects or comorbidities, are not taken into account when calculating the annual treatment costs.

On brolucizumab: Treatment with brolucizumab is initiated with three injections at an interval of 4 weeks. Alternatively, two injections can be administered at an interval of 6 weeks to initiate therapy and, if necessary, a third injection at week 12. After initiation of therapy, treatment every 12 weeks should be considered for patients without disease activity and every 8 weeks for patients with disease activity.

On aflibercept 2 mg: Treatment with aflibercept is initiated with three consecutive monthly injections; followed by a treatment interval of two months. Then, this treatment interval can be maintained or prolonged by 2 - 4 weeks in a "Treat & Extend" dosage regimen. Treatment intervals longer than 4 months were not investigated. This has no effect on the cost calculation, as prolongation of the dosing interval beyond 4 months is still possible according to the product information. If the functional and/or morphological findings deteriorate, the treatment interval should be shortened accordingly. Treatment intervals below 4 weeks were not studied. To calculate the upper limit of treatments, the 2-month treatment interval achieved according to the fixed initial scheme is taken as a basis.

On faricimab: According to the specifications in the product information, the treatment is initiated with four injections at intervals of 4 weeks. After 20 and/or 24 weeks, a treatment check-up is suggested, on the basis of which the physician can individually determine the treatment intervals based on the disease activity. In patients without disease activity, administering faricimab every 16 weeks is to be considered. For patients with disease activity, treatment every 8 weeks or 12 weeks is to be considered.

On ranibizumab: Treatment in adults starts with one injection per month until maximum visual acuity is achieved and/or there are no more signs of disease activity. Initially, three or more injections may be necessary. Finally, patients can be treated according to a "treat & extend" regimen, whereby the treatment interval can be extended by up to two weeks at a time.

The information on treatment costs refers to the application on one eye. Treatment of the second eye is possible.

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 varies from patient to patient 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 the maximum treatment duration, if specified in the product information. Any treatment intervals specified in other time units in the respective product information are converted to "days". A year corresponds to 365 days, a month corresponds to 30.4 days and a week corresponds to 7 days.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Brolucizumab 1st year	1 x every 4 weeks for 3 applications Alternative: 1 x every 6 weeks for 2 applications, if necessary 1 x application in week 12	2 - 3	1	5 - 8
	Then 1 x every 8 - 12 weeks	3 - 5		
Brolucizumab Subsequent years	1 x every 8 – 12 weeks	4.3 - 6.5	1	4.3 – 6.5
Appropriate comparator therapy				
Aflibercept 1st year	1 x monthly[2] for 3 applications, then 1 x every 2 months	3 1	1	6 - 7
	1 x every 2 months until Treat & Extend[3]	2 - 3		

2 One month corresponds to 30.4 days.
3 To calculate the lower limit: The dosing interval can be extended by 14 or 28 days after each treatment.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Aflibercept Subsequent years	1 x every 2 months until Treat & Extend[3]	0 - 6.0	1	0 - 6.0
Faricimab 1st year	1 x every 4 weeks for 4 applications	4	1	6 - 9
	1 x every 8 – 16 weeks	2 - 5		
Faricimab Subsequent years	1 x every 8 – 16 weeks	3.3 – 6.5	1	3.3 – 6.5
Ranibizumab 1st year	1 x monthly[2] for 3 applications,	3	1	7 - 12
	1 x monthly[2] until Treat & Extend[4]	4 - 9		
Ranibizumab Subsequent years	1 x monthly[2] until Treat & Extend[4]	0 - 12.0	1	0 - 12.0

4 To calculate the lower limit: The dosing interval can be extended by a maximum of 2 weeks after each treatment.

Consumption:

Designation of the therapy	Dosage/ Application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Brolucizumab 1st year	6 mg	6 mg	1 x 6 mg	5 – 8	5 x 6 mg – 8 x 6 mg
Brolucizumab Subsequent years	6 mg	6 mg	1 x 6 mg	4.3 – 6.5	4.3 x 6 mg – 6.5 x 6 mg
Appropriate comparator therapy					
Aflibercept 1st year	2 mg	2 mg	1 x 2 mg	6.0 – 7.0	6 x 2 mg – 7 x 2 mg
Aflibercept Subsequent years	2 mg	2 mg	1 x 2 mg	0.0 – 6.0	0 x 2 mg – 6.0 x 2 mg
Faricimab 1st year	6 mg	6 mg	1 x 6 mg	6.0 – 9.0	6.0 x 6 mg – 9.0 x 6 mg
Faricimab Subsequent years	6 mg	6 mg	1 x 6 mg	3.3 – 6.5	3.3 x 6 mg – 6.5 x 6 mg
Ranibizumab 1st year	0.5 mg	0.5 mg	1 x 0.5 mg	7.0 – 12.0	7 x 0.5 mg – 12 x 0.5 mg
Ranibizumab Subsequent years	0.5 mg	0.5 mg	1 x 0.5 mg	0.0 – 12.0	0 x 0.5 mg – 12.0 x 0.5 mg

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 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					
Brolucizumab	1 SFI	€ 984.86	€ 2.00	€ 53.90	€ 928.96
Appropriate comparator therapy					
Aflibercept	1 SFI	€ 1,099.42	€ 2.00	€ 60.24	€ 1,037.18
Faricimab	1 SFI	€ 970.93	€ 2.00	€ 53.13	€ 915.80
Ranibizumab	1 SFI	€ 1,022.77	€ 2.00	€ 56.00	€ 964.77
Abbreviations: SFI = solution for injection					

LAUER-TAXE® last revised: 15 April 2024

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.

Additionally required SHI services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information and package information leaflet are given by the treatment costs of the intravitreal injections and the necessary postoperative checks.

All four active ingredients are applied by intravitreal injection. For intravitreal injections, GOPs of the EBM are available [GOP 31371/ 36371 (right eye), GOP 31372/ 36372 (left eye) or GOP 31373/ 36373 (both eyes)].

Visual acuity checks are included in the basic specialist flat rate.

The product information for brolucizumab, aflibercept, faricimab and ranibizumab recommend setting the treatment interval based on disease activity as determined by morphological parameters and/or visual acuity or functional findings.

The check-up interval should be determined by the attending physician, this can be more frequent than the injection interval.

Costs are incurred for the check-ups carried out for all treatment options. Among others, there are GOPs of the EBM for optical coherence tomography (OCT) for therapy control [GOP 06338

(right eye) or GOP 06339 (left eye)]. The frequency and type of examination used can vary from patient to patient. Due to the individual specification of the control intervals by the attending physician, the costs incurred cannot be quantified.

Type of service	Costs/ service	Number/ year	Costs/ year
Medicinal product to be assessed			
Brolucizumab			
Intravitreal administration of the medicinal product to the left or right eye (EBM 31372/ 36372 or 31371/ 36371)	€ 92.85 - € 198.70	1st year: 5 – 8 Subsequent years: 4.3 – 6.5	1st year: € 464.25 - € 1,589.60 Subsequent years: € 399.26 - € 1,291.55
Optical coherence tomography (EBM 06338 or 06339)	€ 48.21	Different from patient to patient	non-quantifiable
Postoperative treatment (EBM 31717 or 31716)	€ 19.93 - € 27.81	1st year: 5 – 8 Subsequent years: 4.3 – 6.5	1st year: € 99.65 - € 222.48 Subsequent years: € 85.70 - € 180.77
Further check-ups	non-quantifiable	Different from patient to patient	non-quantifiable
Appropriate comparator therapy			
Aflibercept			
Intravitreal administration of the medicinal product to the left or right eye (EBM 31372/ 36372 or 31371/ 36371)	€ 92.85 - € 198.70	1st year: 6 – 7 Subsequent years: 0 – 6.0	1st year: € 557.10 - € 1,390.90 Subsequent years: € 0 - € 1,192.20
Postoperative treatment (EBM 31717 or 31716)	€ 19.93 - € 27.81	1st year: 6 – 7 Subsequent years: 0 – 6.0	1st year: € 119.58 - € 194.67 Subsequent years: € 0 - € 166.86
Optical coherence tomography (EBM 06338 or 06339)	€ 48.21	Different from patient to patient	non-quantifiable
Further check-ups	non-quantifiable	Different from patient to patient	non-quantifiable
Faricimab			

Type of service	Costs/ service	Number/ year	Costs/ year
Intravitreal administration of the medicinal product to the left or right eye (EBM 31372/ 36372 or 31371/ 36371)	€ 92.85 - € 198.70	1st year: 6.0 – 9.0 Subsequent years: 3.3 – 6.5	1st year: € 557.10 - € 1,788.30 Subsequent years: € 306.41 - € 1,291.55
Postoperative treatment (EBM 31717 or 31716)	€ 19.93 - € 27.81	1st year: 6.0 – 9.0 Subsequent years: 3.3 – 6.5	1st year: € 119.58 - € 250.29 Subsequent years: € 65.77 - € 180.77
Optical coherence tomography (EBM 06338 or 06339)	€ 48.21	Different from patient to patient	non-quantifiable
Ranibizumab			
Intravitreal administration of the medicinal product to the left or right eye (EBM 31372/ 36372 or 31371/ 36371)	€ 92.85 - € 198.70	1st year: 7 – 12 Subsequent years: 0 – 12.0	1st year: € 649.95 - € 2,384.40 Subsequent years: € 0 - € 2,384.40
Postoperative treatment (EBM 31717 or 31716)	€ 19.93 - € 27.81	1st year: 7 – 12 Subsequent years: 0 – 12.0	1st year: € 139.51 - € 333.72 Subsequent years: € 0 - € 333.72
Optical coherence tomography (EBM 06338 or 06339)	€ 48.21	Different from patient to patient	non-quantifiable
Further check-ups	non-quantifiable	Different from patient to patient	non-quantifiable

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Adults with neovascular (wet) age-related macular degeneration (AMD)

- No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:

Product information for brolucizumab (Beovu); Beovu 120 mg/ml solution for injection in a

pre-filled syringe, Beovu 120 mg/ml solution for injection; last revised: July 2023

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 June 2015, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 18 October 2023, the pharmaceutical company submitted a dossier for the benefit assessment of brolucizumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 5 VerfO.

By letter dated 20 October 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 brolucizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 December 2023, and the written statement procedure was initiated with publication on the G-BA website on 01 February 2024. The deadline for submitting statements was 22 February 2024.

The oral hearing was held on 11 March 2024.

By letter dated 18 March 2024, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 12 April 2024.

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 23 April 2024, and the proposed resolution was approved.

At its session on 2 May 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	23 June 2015	Implementation of the appropriate comparator therapy.
Working group Section 35a	5 March 2024	Information on written statements received, preparation of the oral hearing.
Subcommittee Medicinal products	11 March 2024	Conduct of the oral hearing Commissioning of the IQWiG with the supplementary assessment of documents.
Working group Section 35a	19 March 2024 16 April 2024	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure.
Subcommittee Medicinal products	23 April 2024	Concluding discussion of the draft resolution.
Plenum	2 May 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive.

Berlin, 2 May 2024

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

Prof. Hecken