Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Brolucizumab (Neovascular Age-related Macular Degeneration)

of 3 September 2020

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 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 market of the active ingredient brolucizumab 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 March 2020. 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 9 March 2020.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 June 2020 on the website of the G-BA (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. 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 brolucizumab.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has arrived at 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).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with neovascular (wet) age-related macular degeneration

- Ranibizumab or aflibercept

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 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. 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 applications or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee 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. There is a marketing authorisation for ranibizumab, aflibercept, and pegaptanib (no longer for sale) 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 (CNV)”.

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

On 2. The following non-medicinal treatment options are available for this therapeutic indication: Photodynamic therapy (PDT), photocoagulation by laser, proton therapy for age-related macular degeneration (resolution of 17 September 2009), photodynamic therapy (PDT) with verteporfin for age-related wet macular degeneration with subfoveolar classic choriodic neovascularisation (resolution of 21 February 2006).

On 3. For aflibercept, there is a resolution of the G-BA from 6 June 2013 in the therapeutic indication under consideration: The additional benefit of aflibercept for the treatment of adults with neovascular (wet) AMD compared with the appropriate comparator therapy ranibizumab is not proven. Furthermore, there is a resolution on proton therapy for age-related macular degeneration dated 17 September 2009 in which no robust indication for a benefit of proton therapy for age-related macular degeneration was found.

On 4. The general state of medical knowledge on which the decision of the G-BA is based was illustrated by systematic research for guidelines and reviews of clinical studies in the present indication. Based on the aggregated evidence, it can be concluded that, according to the guideline recommendations, the standard therapy for the targeted treatment situation consists of treatment with a VEGF inhibitor without a clear superiority of a specific inhibitor available in Germany. Ranibizumab, aflibercept, and pegaptanib are approved for the relevant therapeutic indication. Pegaptanib is not available in Germany because distribution has been discontinued. It also plays a subordinate role in the aggregated evidence.

Against the background of the aggregated evidence in the indication, the importance of non-medicinal interventions is considered to be lower compared with VEGF inhibitors .

In the overall view, aflibercept or ranibizumab in adults with neovascular (wet) age-related macular degeneration (AMD) is therefore determined to be an appropriate comparator therapy.

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

2.1.3 Extent and probability of the additional benefit

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

For adults with neovascular (wet) age-related macular degeneration, the additional benefit is not proven.

Justification:

No data are available to assess the additional benefit compared with the appropriate comparator therapy.

The pharmaceutical company identified 5 randomised controlled trials (RCT) with brolucizumab compared with aflibercept or ranibizumab: SEE (C-10-083), OSPREY (C-12-006), HAWK (RTH258-C001), HARRIER (RTH258-C002), and TALON (CRTH258A2303). Data are not yet available for the TALON study. In the other studies, the active ingredients aflibercept or ranibizumab were not used according to the marketing authorisation. The pharmaceutical company has therefore excluded the studies from the benefit assessment and does not provide data for the assessment of the additional benefit.

In the double-blind SEE RCT with a study duration of 6 months, brolucizumab was compared with ranibizumab. Both active ingredients were injected only once; no further treatment

intervals were planned in the study protocol. However, according to the product information of ranibizumab information leaflet, monthly treatment should be continued until maximum visual acuity is achieved and/or no signs of disease activity are observed. The appropriate comparator therapy has therefore not been implemented in the SEE study.

The OSPREY, HAWK, and HARRIER studies compared brolucizumab with aflibercept. In these studies, aflibercept was administered every 8 weeks after an initiation phase in which aflibercept was injected once a month for 3 months. On the other hand, the product information stipulates an individual adjustment of the treatment interval based on functional and/or morphological findings.

Thus, in none of the studies identified was the appropriate comparator therapy used according to the product information. There are thus no data from which the additional benefit of brolucizumab compared with ranibizumab or aflibercept can be derived. The additional benefit is therefore not proven.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of brolucizumab has its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

The resolution is not based on appropriate comparative data of brolucizumab compared with the appropriate comparator therapy. Against the background that comparative clinical data, which are in principle relevant for the benefit assessment of brolucizumab in the present indication, are expected from the ongoing double-blind, multi-centre TALON RCT, it is justified to limit the period of validity of the present resolution. The TALON study compares brolucizumab with aflibercept over a treatment period of 64 weeks. According to the pharmaceutical company, the study should be completed in Q1 2023.

The results of the TALON study on brolucizumab compared with the appropriate comparator therapy should be presented in the dossier for the renewed benefit assessment after the expiration of the limitation period. A limitation of the resolution until 1 November 2023 is considered to be appropriate. The G-BA is able, in principle, to revise the limitation if it has been presented with clear justification that it is insufficient or too long. In accordance with Section 3, paragraph 1, No. 5 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, No. 7 VerfO, the procedure for the benefit assessment for the medicinal product brolucizumab shall recommence when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the day of expiry of the deadline to prove the extent of the additional benefit of brolucizumab (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5, Section 8, number 5 VerfO). The possibility that a benefit assessment for brolucizumab can be carried out for other reasons (*cf* Chapter 5, Section 1, paragraph 2 VerfO) remains unaffected.

2.1.5 Summary of the assessment

This assessment refers to the benefit assessment of the new medicinal product Beovu® with the active ingredient brolucizumab. Brolucizumab is approved for the treatment of neovascular (wet) age-related macular degeneration (AMD) in adults.

Aflibercept or ranibizumab was determined by the G-BA to be an appropriate comparator therapy for brolucizumab.

The pharmaceutical company identified 5 randomised controlled trials with brolucizumab compared with aflibercept or ranibizumab: SEE (C-10-083), OSPREY (C-12-006), HAWK (RTH258-C001), HARRIER (RTH258-C002), and TALON (CRTH258A2303). Data are not yet available for the TALON study. In the other studies, the active ingredients aflibercept or ranibizumab were not used according to the marketing authorisation. The pharmaceutical company has therefore excluded the studies from the benefit assessment and does not provide data for the assessment of the additional benefit.

The additional benefit of brolucizumab compared with the appropriate comparator therapy is therefore not proven.

The resolution is limited until 1 November 2023.

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

The information on patient numbers is based on the target population in statutory health insurance (SHI).

The G-BA bases its resolution on the information from the dossier of the pharmaceutical company. The calculation used to derive patient numbers is comprehensible, and the magnitude of the figures arrived at are plausible. Because of the uncertain data basis, the specification of a range is generally appropriate for estimating the SHI target population 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: 10 June 2020):

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

Brolucizumab may be administered only by a qualified ophthalmologist experienced in the performance and after-care of intravitreal injections.

Officially approved informational materials on risk minimisation are available for the medicinal product.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 August 2020).

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”, the time between individual treatments, and for maximum treatment duration if specified in the product information.

Because of the patient-individual procedure regarding the adjustment of the treatment intervals as specified in the product information, only the possible upper and lower limits of the costs for the first year of treatment are presented in this resolution.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

On brolucizumab: According to the information given in the product information, treatment is initiated with three injections at intervals of 4 weeks. After 16 weeks, a treatment control is suggested. Treatment every 12 weeks for patients without disease activity and every 8 weeks for patients with disease activity should then be considered.

On ranibizumab: Treatment in adults begins with one injection per month until maximum visual acuity is achieved and/or no signs of disease activity are observed. Initially, 3 or more injections may be required. Finally, patients can be treated according to a “treat & extend” scheme, whereby the treatment interval should not be extended more than 2 weeks at a time.

On aflibercept Treatment with aflibercept is initiated with three consecutive monthly injections followed by a treatment interval of two months. This treatment interval can be maintained or extended by 2–4 weeks in a “treat & extend” dosing scheme.

The information on treatment costs refers to the application on a single eye. A treatment of the second eye is not possible.

Treatment duration:

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	1 × every 28 days for 3 applications	3	1	5.7–7.5
	then every 56 – 84 days	4.5 – 2.7		
Appropriate comparator therapy				
Aflibercept	1 × monthly[1] for 3 applications then 1 × every 2 months[1]	4	1	6.3–7.0
	Afterwards 1 × every 2 months[1] – Treat & extend [2] (28 days)	3 – 2.3		
Ranibizumab	1 × monthly[1] for 3 applications	3	1	7.1–12
	Afterwards 1 × monthly[1] – Treat & extend (14 days)[3]	9– 4.1		

[1] One month corresponds to 30.4 days.
[2] To calculate the lower limit: The treatment interval is extended by 4 weeks with each treatment.
[3] To calculate the lower limit: The treatment interval is extended by 2 weeks with each treatment.

Usage and 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	6 mg	6 mg	1 × 6 mg	7.5–	7.5 × 6 mg –
				5.7	5.7 × 6 mg
Appropriate comparator therapy					
Aflibercept	2 mg	2 mg	1 × 2 mg	7.0–	7.0 × 2 mg –
				6.3	6.3 × 2 mg
Ranibizumab	0.5 mg	0.5 mg	1 × 0.5 mg	12–	12 × 0.5 mg –
				7.1	7.1 × 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 Sections 130 and 130 a 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 product:

Designation of the therapy	Package 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	€ 1,107.64	€ 1.77	€ 62.30	€ 1,043.57
Appropriate comparator therapy					
Aflibercept	1 SFI	€ 1,071.43	€ 1.77	€ 60.24	€ 1,009.42
Ranibizumab	1 SFI	€ 1,231.18	€ 1.77	€ 69.32	€ 1,160.09
Abbreviations: SFI = solution for injection					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 August 2020

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 assessed 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 usual expenditure in the course of the treatment are not shown.

Additionally required SHI services for the use of the medicinal product to be assessed and the appropriate comparator therapy according to the product and package information are given by the treatment costs of intravitreal injections as well as the necessary postoperative controls.

All three active ingredients are applied by intravitreal injection. For intravitreal injection, fee schedules (GOP) of the EBM are available (GOP 31371/36371 (right eye), GOP 31372/36372 (left eye) or GOP 31373/36373 (both eyes)).

The visual acuity checks are included in the basic lump sum for specialists.

The product information of brolucizumab, ranibicumab, and aflibercept recommends that the treatment interval be based on disease activity. This is determined by morphological parameters and/or visual acuity or functional findings. The control interval should be determined by the attending doctor; this can be more frequent than the injection interval.

For all therapy options, costs are incurred for the control examinations performed. Among others, GOP of the EBM for optical coherence tomography (OCT) for therapy control are available (GOP 06338 (right eye) or GOP 06339 (left eye). The frequency and type of examination used may vary from patient to patient. Because of the individual determination of the control intervals by the attending doctor, the resulting costs cannot be quantified.

Type of service	Cost/service	Number/year	Costs/year
Medicinal product to be assessed			
Brolucizumab			
Intravitreal drug administration in the left or right eye (EBM 31372/ 36372 or 31371/ 36371)	€ 88.67 – 184.91	5.7–7.5	€ 505.42 – 1,386.83
Postoperative treatment (EBM 31717 or 31716)	€ 18.35 – 25.60	5.7–7.5	€ 104.60 – 192
Optical coherencetomography (EBM 06338 or 06339)	€ 44.39	different for each individual patient	Non-quantifiable
Other control examinations	Non-quantifiable	different for each individual patient	Non-quantifiable
Appropriate comparator therapy			
Aflibercept			
Intravitreal drug administration in the left	€ 88.67 – 184.91	6.3–7.0	€ 558.62 – 1,294.37

or right eye (EBM 31372/ 36372 or 31371/ 36371)			
Postoperative treatment (EBM 31717 or 31716)	€ 18.35 – 25.60	6.3–7.0	€ 115.61 – 179.20
Optical coherencetomography (EBM 06338 or 06339)	€ 44.39	different for each individual patient	Non-quantifiable
Further control examinations	Non-quantifiable	different for each individual patient	Non-quantifiable
Ranibizumab			
Intravitreal drug administration in the left or right eye (EBM 31372/ 36372 or 31371/ 36371)	€ 88.67 – 184.91	7.1–12	€ 629.56 – 2,218.92
Postoperative treatment (EBM 31717 or 31716)	€ 18.35 – 25.60	7.1–12	€ 130.29 – 307.20
Optical coherencetomography (EBM 06338 or 06339)	€ 44.39	different for each individual patient	Non-quantifiable
Further control examinations	Non-quantifiable	different for each individual patient	Non-quantifiable

3. Bureaucratic costs

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 9 March 2020, 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 1, sentence 2 VerfO.

By letter dated 10 March 2020 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 brolucizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 10 June 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 15 June 2020. The deadline for submitting written statements was 6 July 2020.

The oral hearing was held on 27 July 2020.

On 28 July 2020, the IQWiG submitted a new version of the IQWiG dossier assessment to the G-BA. Version 1.1 of 28 July 2020 replaces version 1.0 of the dossier assessment of 10 June 2020. The evaluation result was not affected by the changes in version 1.1 compared with version 1.0.

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 25 August 2020, and the proposed resolution was approved.

At its session on 3 September 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	23 June 2015	Determination of the appropriate comparator therapy
Working group Section 35a	22 July 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	27 July 2020	Conduct of the oral hearing
Working group Section 35a	5 August 2020 19 August 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	25 August 2020	Concluding discussion of the draft resolution
Plenum	3 September 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 3 September 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken