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
Faricimab (Diabetic macular oedema)

of 6 April 2023

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 online and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient faricimab on 15 October 2022 in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. 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 13 October 2022.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 16 January 2023 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 faricimab 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 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 faricimab.

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 Faricimab (Vabysmo) in accordance with the product information

Vabysmo is indicated for the treatment of adult patients with:

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

Therapeutic indication of the resolution (resolution of 06.04.2023):

Vabysmo is indicated for the treatment of adult patients with visual impairment due to diabetic macular oedema (DME).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with visual impairment due to diabetic macular oedema (DME)

Appropriate comparator therapy for faricimab:

- Aflibercept or ranibizumab

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 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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.

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

on 1. In the present therapeutic indication, besides the marketing authorisation for faricimab, a marketing authorisation for ranibizumab, aflibercept, brolucizumab, dexamethasone and fluocinolone is present for the treatment of visual impairment due to DME.

on 2. The following non-medicinal treatment options are available in the present therapeutic indication: in the case of an additionally present vitreomacular traction, there is the possibility of a vitrectomy.

on 3. In the therapeutic indication under consideration, there are G-BA resolutions of 14 September 2014 for aflibercept and of 20 October 2022 for brolucizumab.

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 therapeutic indication. 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.

For the derivation of the appropriate comparator therapy in the present therapeutic indication, it is assumed that patients with visual impairment due to DME show foveal involvement. It is also assumed that clinically significant macular oedema is present according to ETDRS criteria.

In the overall assessment, a recommendation for therapy with a VEGF inhibitor can be derived from the aggregated evidence according to the guideline recommendations in the treatment setting targeted here, without a clear superiority of a specific VEGF inhibitor available in Germany having been shown to date. In the relevant therapeutic indication, ranibizumab, aflibercept and brolucizumab are approved as VEGF inhibitors.

The significance of non-medicinal measures is considered to be lower than that of VEGF inhibitors for the treatment of visual impairment due to DME in light of the aggregated evidence. The same applies to the possible use of approved, intravitreally applied steroid implants with dexamethasone or fluocinolone; the latter are also not approved for the first-line treatment of DME.

The active ingredient brolucizumab is a new treatment option in the present therapeutic indication. The active ingredient was only recently approved for the indication of visual impairment due to diabetic macular oedema (DME) in adults (marketing authorisation on 28.03.2022). In addition, no additional benefit of brolucizumab compared to aflibercept was identified by resolution of 20 October 2022. Based on the generally accepted state of medical knowledge, brolucizumab is not determined to be an appropriate comparator therapy for the present resolution.

In the overall assessment, the G-BA therefore considers it appropriate to designate the VEGF inhibitors aflibercept or ranibizumab as the appropriate comparator therapy for the treatment of adults with visual impairment due to DME.

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

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

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 faricimab is assessed as follows:

For adults with visual impairment due to DME, the additional benefit of faricimab over aflibercept is not proven.

Justification:

The benefit assessment is based on the two double-blind, randomised, active controlled RHINE and YOSEMITE studies as well as the meta-analysis of both studies at week 1 of the year.

The RHINE and YOSEMITE studies are randomised, double-blind phase III studies comparing faricimab versus aflibercept. Both studies enrolled adults with type 1 or type 2 diabetes mellitus (HbA1c ≤ 10% within 2 months prior to the start of treatment) and visual impairment due to DME. Both studies were also able to enrol patients who had been pretreated with VEGF inhibitors, provided that no intravitreal anti-VEGF therapy had taken place within 3 months prior to the start of treatment.

One eye was selected as the eye under study. The best corrected visual acuity (BCVA) of the eye under study, using Early Treatment Diabetic Retinopathy Study (ETDRS) eye charts, had to be between 73 and 25 ETDRS letters at a distance of 4 metres. In addition, retinal oedema involving the fovea had to be present in the eye under study. If both eyes were suitable, the eye with the worse visual acuity was selected as the eye under study. However, the principal investigator could also select the eye with the better visual acuity if this eye was considered more suitable for treatment with the study medication. In approximately 10% (RHINE) and 9% (YOSEMITE) of the patients, both eyes met the inclusion criteria of the studies, and of these, the eye with the better visual acuity was selected as the eye under study in approximately one-third (without indicating the specific reasons).

In the RHINE study, a total of 951 patients and in the YOSEMITE study, 940 patients were randomised in a 1:1:1 ratio to the following study arms:

- Faricimab at 4-week intervals until week 20 followed by 8-week intervals (Q8W)
- Faricimab at 4-week intervals until at least week 12 followed by individual adjustment of the injection intervals (personalised treatment interval, PTI)
- Aflibercept at 4-week intervals until week 20 followed by 8-week intervals (Q8W)

In the faricimab PTI arm of both studies, patients received faricimab according to the requirements in the product information. In the faricimab Q8W arm, there was no flexibilisation of the treatment regimen based on the physician's assessment of the anatomical and/or visual findings ("*Treat and Extend*") according to the product information. Therefore, in accordance with the assessment of the pharmaceutical company, the faricimab Q8W arm is not relevant for the present benefit assessment.

The product information for aflibercept was amended in December 2022. According to the current product information, treatment with aflibercept is initiated with five consecutive monthly injections, followed by one injection every two months. This treatment interval can now be directly adjusted according to a "*Treat and Extend*" dosing scheme individually in two-week steps. According to the product information that was valid before this change, flexibilisation of the treatment interval was only possible after twelve months. The present benefit assessment was based on the product information that was valid before the amendment in December 2022.

Treatment with aflibercept was initiated in each of the RHINE and YOSEMITE studies with five consecutive monthly injections, followed by one injection every two months. The treatment interval could be individually adjusted according to a "*Treat and Extend*" dosing scheme after the first 12 months of treatment, according to the product information of aflibercept valid prior to the change in December 2022. Such an individual determination of the treatment intervals was not planned in either study after the first year of treatment. In deviation from the pharmaceutical company's procedure, only the comparative analyses for year 1 are therefore taken into account for the present benefit assessment.

Extent and probability of the additional benefit

Mortality

For the endpoint of overall mortality, there is a statistically significant difference to the advantage of faricimab in the RHINE study. In the YOSEMITE study as well as the meta-analyses of both studies, no statistically significant difference was detected between the treatment groups.

Morbidity

Best Corrected Visual Acuity (BCVA) - improvement of ≥ 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 avoidance of deterioration of BCVA. For the present benefit assessment, the responder analyses for improvement by ≥ 10 ETDRS letters (corresponding to 2 lines) or for improvement by ≥ 15 ETDRS letters (corresponding to 3 lines) are used.

For the endpoint of BCVA (improvement by ≥ 10 as well as ≥ 15 ETDRS letters), there was no statistically significant difference between the treatment groups, neither at the individual study level nor in the meta-analysis of both the RHINE and YOSEMITE studies.

NEI VFQ-25 (general health status subscale)

For the endpoint of health status (assessed via NEI VFQ-25, general health status subscale), there was no statistically significant difference between the treatment groups, neither at the individual study level nor in the meta-analysis of the two studies RHINE and YOSEMITE.

Quality of life

National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) – Sum Score

Quality of life was assessed in both studies using the NEI VFQ-25. 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 sum score is calculated from the mean of the averaged scores of the subscales. The item / subscale on general health is not included. The sum score can take values between 0 and 100, with higher values indicating a better visual acuity-related quality of life.

The pharmaceutical company submits responder analyses for the improvement of the sum score of the NEI VFQ-25 and the 12 subscales by ≥ 15 points each. Patients were considered responders if they met the response criterion at least one visit up to week 56. The NEI VFQ-25 was collected during this period on day 1, at week 24 and week 52 or at premature study discontinuation. Thus, responder analyses, in which only those patients who showed an improvement of ≥ 15 points in the sum score or the subscale scores at week 52 were evaluated as responders, are not available. Therefore, the continuous evaluations are used for the present assessment.

For the endpoint of health-related quality of life (assessed by the sum score of the NEI VFQ-25), the meta-analysis of the RHINE and YOSEMITE studies as well as both individual studies showed no statistically significant difference between the treatment groups.

Side effects

SAEs, discontinuation due to AEs, ocular AEs and ocular SAEs

For the endpoints of SAEs, discontinuation due to AEs, ocular AEs and ocular SAEs, the meta-analysis of the RHINE and YOSEMITE studies as well as both individual studies showed no statistically significant difference between the treatment groups.

<u>Overall assessment/ conclusion</u>

For the assessment of the additional benefit of faricimab, evaluations of the two double-blind, randomised, active controlled phase III studies RHINE and YOSEMITE (each versus aflibercept) as well as the meta-analysis of both studies are available at year 1.

In summary, there is no statistically significant difference in mortality between the treatment groups. In the morbidity category, there was also no statistically significant difference between faricimab and aflibercept in the change in best-corrected visual acuity as well as health status.

In the quality of life category, there was no statistically significant difference between faricimab and the appropriate comparator therapy aflibercept for the visual acuity-related quality of life collected using NEI VFQ-25.

In the category of side effects, no advantages or disadvantages relevant to the benefit assessment can be derived for faricimab compared to aflibercept overall.

In the overall assessment, there are neither advantages nor disadvantages of faricimab compared to the appropriate comparator therapy aflibercept for the treatment of visual impairment due to DME on the basis of the studies presented at year 1. An additional benefit

of faricimab compared to the appropriate comparator therapy aflibercept is therefore not proven for adults with visual impairment due to DME.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Vabysmo with the active ingredient faricimab.

Faricimab is indicated for the treatment of adults with visual impairment due to diabetic macular oedema (DME).

The G-BA determined aflibercept or ranibizumab as the appropriate comparator therapy.

For the assessment of the additional benefit, the pharmaceutical company submits the two RCTs RHINE and YOSEMITE as well as the meta-analysis of both studies at year 1, in each of which faricimab was compared with aflibercept.

In summary, there is no statistically significant difference in mortality between the treatment groups. In the morbidity category, there was also no statistically significant difference between faricimab and aflibercept in the change in best-corrected visual acuity as well as health status. There is also no statistically significant difference between faricimab and aflibercept in the category of quality of life in the surveyed, visual acuity-related quality of life. In the category of side effects, no advantages or disadvantages relevant for the benefit assessment can be derived overall.

In the overall assessment, there are no advantages or disadvantages of faricimab compared with the appropriate comparator therapy aflibercept. An additional benefit is not proven.

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

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

The patient numbers submitted by the pharmaceutical company with the dossier are uncertain in the lower limit and underestimated in the upper limit. Existing uncertainties could have been taken into account by using a wider range. The resolution is therefore not based on the figures presented in the dossier, but on the figures from the resolution on brolucizumab of 20 October 2022 in the same therapeutic indication.

The derivation of the patient numbers in the dossier on the active ingredient brolucizumab was basically comprehensible; however, within the patients with DME, no percentage values for those with visual impairment due to DME were taken into account. Taking into account the percentage values of 2.56% to 2.64% from the previous benefit assessment procedure in the indication DME[2], IQWIG's own calculation resulted in a number of 190,000 to 241,000 patients in the SHI target population. 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 these uncertainties 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

[2] Resolution on the early benefit assessment of aflibercept in the indication DME of 15.09.2014.

product characteristics, SmPC) for Vabysmo (active ingredient: faricimab) at the following publicly accessible link (last access: 17 January 2023):

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

Treatment with faricimab should only be initiated and monitored by doctors experienced in the therapy of diabetic macular oedema.

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.

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 March 2023).

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 faricimab: According to the specifications in the product information, the treatment is initiated with four injections at intervals of 4 weeks. Subsequently, the treatment is individually adapted depending on the disease activity ("Treat and Extend"). Based on the physician's assessment of the anatomical and/or visual findings, the dosing interval may be extended in increments of up to 4 weeks to up to 16 weeks.

On aflibercept: Treatment with aflibercept is initiated with five consecutive monthly injections, followed by a treatment interval of two months. Then, this treatment interval can be maintained or prolonged usually by 2 weeks in a "Treat & Extend" dosing scheme. Limited data are available for treatment intervals longer than 4 months. 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 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 one month 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.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Faricimab 1st year	1 x every 28 days for 4 applications	4	1	7.0 - 13.0
	then every 28 to 112 days according to Treat & Extend	9 - 3		
Faricimab Subsequent years	Then, every 28 to 112 days	13.0 - 3.3	1	3.3 - 13.0
Appropriate comparator therapy				
aflibercept 1st year	1 x monthly[3] for 5 applications and 1 x every 2 months[3] for an application,	5 1	1	7.0 - 8.0
	Then, 1 x every 2 months[3] until Treat & Extend (30.4 days)[4]	2 - 1		
aflibercept Subsequent years	1 x every 2 months[3] until Treat & Extend (30.4 days)[4]	6 - 0	1	0 - 6.0
Ranibizumab 1st year	1 x monthly[3] for 3 applications,	3	1	6.0 - 12.0
	Then, 1 x monthly[3] until Treat & Extend (30.4 days)[5]	9 - 3		
Ranibizumab subsequent years	1 x monthly[3]	12 - 0	1	0 - 12.0

[3] One month corresponds to 30.4 days.
[4] To calculate the lower limit: The treatment interval is prolonged by half a month for each treatment.
[5] To calculate the lower limit: The treatment interval is prolonged by one month for each treatment.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	until Treat & Extend (30.4 days)[5]			

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					
Faricimab 1st year	6 mg	6 mg	1 x 6 mg	7.0 - 13.0	7.0 x 6 mg - 13.0 x 6 mg
Faricimab Subsequent years	6 mg	6 mg	1 x 6 mg	3.3 - 13.0	3.3 x 6 mg - 13.0 x 6 mg
Appropriate comparator therapy					
aflibercept 1st year	2 mg	2 mg	1 x 2 mg	7.0 - 8.0	7.0 x 2 mg - 8.0 x 2 mg
aflibercept Subsequent years	2 mg	2 mg	1 x 2 mg	0 - 6.0	0 x 2 mg - 6.0 x 2 mg
Ranibizumab 1st year	0.5 mg	0.5 mg	1 x 0.5 mg	6.0 - 12.0	6.0 x 0.5 mg - 12.0 x 0.5 mg
Ranibizumab subsequent years	0.5 mg	0.5 mg	1 x 0.5 mg	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					
Faricimab	1 SFI	€ 1,136.52	€ 2.00	€ 106.80	€ 1,027.72
Appropriate comparator therapy					
aflibercept	1 SFI	€ 1,099.38	€ 2.00	€ 103.28	€ 994.10
Ranibizumab	1 SFI	€ 1,263.26	€ 2.00	€ 118.83	€ 1,142.43
Abbreviations: SFI = solution for injection					

LAUER-TAXE® last revised: 15 March 2023

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 three 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 faricimab, aflibercept and ranibizumab recommends 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	Cost/ service	Number/ year	Cost/ year
Medicinal product to be assessed			
Faricimab			
Intravitreal administration of the medicinal product to the left or right eye (EBM 31372/ 36372 or 31371/ 36371)	€ 89.40 - € 191.33	1st year: 7 - 13 Subsequent years: 3.3 - 13	1st year: € 625.80 - € 2,487.29 Subsequent years: € 295.02 - € 2,487.29
Postoperative treatment (EBM 31717 or 31716)	€ 19.19 - € 26.78	1st year: 7 - 13 Subsequent years: 3.3 - 13	1st year: € 134.33 - € 348.14 Subsequent years: € 63.33 - € 348.14
Optical coherence tomography (EBM 06338 or 06339)	€ 46.43	Varies from patient to patient	non-quantifiable
Further check-ups	non-quantifiable	Varies 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)	€ 89.40 - € 191.33	1st year: 7 - 8 Subsequent years: 0 - 6	1st year: € 625.80 - € 1,530.64 Subsequent years: € 0 - € 1,147.98
Postoperative treatment (EBM 31717 or 31716)	€ 19.19 - € 26.78	1st year: 7 - 8 Subsequent years: 0 - 6	1st year: € 134.33 - € 214.24 Subsequent years: € 0 - € 160.68
Optical coherence tomography (EBM 06338 or 06339)	€ 46.43	Varies from patient to patient	non-quantifiable
Further check-ups	non-quantifiable	Varies 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)	€ 89.40 - € 191.33	1st year: 6 - 12 Subsequent years: 0 - 12	1st year: € 536.40 - € 2,295.96 Subsequent years: € 0 - € 2,295.96
Postoperative treatment (EBM 31717 or 31716)	€ 19.19 - € 26.78	1st year: 6 - 12 Subsequent years: 0 - 12	1st year: € 115.14 - € 321.36 Subsequent years: € 0 - € 321.36

Type of service	Cost/ service	Number/ year	Cost/ year
Optical coherence tomography (EBM 06338 or 06339)	€ 46.43	Varies from patient to patient	non-quantifiable
Further check-ups	non-quantifiable	Varies from patient to patient	non-quantifiable

2.5 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 Faricimab

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate 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.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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 7 April 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 13 October 2022, the pharmaceutical company submitted a dossier for the benefit assessment of faricimab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 14 October 2022 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 faricimab.

The dossier assessment by the IQWiG was submitted to the G-BA on 12 January 2023, and the written statement procedure was initiated with publication on the G-BA website on 16 January 2023. The deadline for submitting written statements was 6 February 2023.

The oral hearing was held on 20 February 2023.

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 28 March 2023, and the proposed resolution was approved.

At its session on 6 April 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	7 April 2021	Determination of the appropriate comparator therapy
Working group Section 35a	15 March 2023	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	20 February 2023	Conduct of the oral hearing
Working group Section 35a	01.03.2023; 15.03.2023; 22.03.2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee on Medicinal Products	28 March 2023	Concluding discussion of the draft resolution
Plenum	6 April 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 6 April 2023

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

Prof. Hecken