Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee 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

At its session on 2 May 2024, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII is amended as follows:

1. The information on brolucizumab in the version of the resolution of 3 September 2020 (Federal Gazette, BAnz AT 01.10.2020 B6) is repealed.
2. Annex XII shall be amended in alphabetical order to include the active ingredient brolucizumab as follows:

Brolucizumab
Resolution of: 2 May 2024
Entry into force on: 2 May 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 13 February 2020):

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).

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

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

Appropriate comparator therapy:

– Aflibercept or faricimab or ranibizumab

Extent and probability of the additional benefit of brolucizumab compared to aflibercept:

An additional benefit is not proven.

Study results according to endpoints:[1]

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

1 Data from the dossier assessment of the IQWiG (A23-101) and from the addendum (A24-31), unless otherwise indicated.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant differences for the benefit assessment.
Morbidity	↔	No relevant differences for the benefit assessment.
Health-related quality of life	↔	No relevant differences for the benefit assessment.
Side effects	↓	Disadvantage in the endpoint of discontinuation due to AEs. In detail, disadvantage in the endpoint of intraocular inflammation.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n.a.: not assessable		

TALON study: RCT, brolucizumab vs aflibercept (at week 32)

Mortality

Endpoint	Brolucizumab		Aflibercept		Brolucizumab vs aflibercept
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
Overall mortality	366	4[b] (1.1)	368	0	9.05 [0.49; 167.47]; 0.045[c]

Morbidity

Endpoint	Brolucizumab		Aflibercept		Brolucizumab vs aflibercept
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
Best corrected visual acuity					
Improvement by ≥ 10 ETDRS letters[d]	366	144 (39.3)	368	131 (35.6)	1.11 [0.92; 1.33]; 0.295
Deterioration by ≥ 10 ETDRS letters[d]	366	22 (6.0)	368	26 (7.1)	0.85 [0.49; 1.47]; 0.564
Improvement by ≥ 15 ETDRS letters[d]	366	88 (24.0)	368	92 (25.0)	0.96 [0.75; 1.24]; 0.763
Deterioration by ≥ 15 ETDRS letters[d]	366	16 (4.4)	368	18 (4.9)	0.89 [0.46; 1.73]; 0.738
NEI VFQ-25[e]					
General health status subscale, improvement by ≥ 15 points	266	47 (17.7)	250	61 (24.4)	0.72 [0.52; 1.02]; 0.062
General health status subscale, deterioration by ≥ 15 points	No data available				

Endpoint	Brolucizumab			Aflibercept			Brolucizumab vs aflibercept
	N[f,g]	Values at the start of study MV (SD)	Change at week 32 MV[h] (SD)	N[f,g]	Values at the start of study MV (SD)	Change at week 32 MV[h] (SD)	MD [95% CI]; p value[h]
NEI VFQ-25[e]							
General health status subscale	n.d.						

Quality of life

Endpoint	Brolucizumab			Aflibercept			Brolucizumab vs aflibercept
	N[f,g]	Values at the start of study MV (SD)	Change at week 32 MV[h] (SD)	N[f,g]	Values at the start of study MV (SD)	Change at week 32 MV[h] (SD)	MD [95% CI]; p value[h]
NEI VFQ-25[e]							
Sum score[i]	278	n.d.	4.09	261	n.d.	3.72	0.37 [-0.2; 0.9]; 0.193

Side effects

Endpoint	Brolucizumab		Aflibercept		Brolucizumab vs aflibercept
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
AEs[j] *(presented additionally)*	366	200 (54.6)	368	200 (54.3)	-
SAEs	366	39 (10.7)	368	31 (8.4)	1.26 [0.81; 1.98]; 0.305
Discontinuation due to AEs	366	18 (4.9)	368	3 (0.8)	6.03 [1.79; 20.31]; 0.004
intraocular inflammation[k,l]	366	20 (5.5)	368	4 (1.1)	5.03 [1.74; 14.56]; < 0.001[c]
Severe intraocular inflammation[l,m]	366	8 (2.2)	368	2 (0.5)	4.02 [0.86; 18.81]; 0.057[c]

a. Wald test
b. 2 patients died from cardiac disorders (cardiac arrest and acute myocardial infarction) and 2 in connection with COVID-19.
c. IQWiG's own calculation, unconditional exact test (CSZ method)
d. Percentage of patients with an increase or decrease of best corrected visual acuity by ≥ 10 ETDRS letters or ≥ 15 ETDRS letters respectively compared to the start of study at week 32 with a scale range from 0 to 100.
e. Higher (increasing) values mean better symptomatology/ health-related quality of life; positive effects (intervention minus control) mean an advantage for the intervention (scale range 0 to 100).
f. Number of patients who were taken into account in the evaluation for calculating the effect estimate; the values at start of study can be based on other patient numbers.
g. Discrepancy between information in the subsequently submitted Annex and Module 5. The data presented are from Module 5.
h. Pairwise ANCOVA model with the treatment as fixed effect factor and the corresponding baseline value of the endpoint as covariate.

i. The following subscales were recorded: General vision, eye pain, near vision, distance vision, social functioning, psychological well-being, performance of social roles, dependence on others, problems with driving a car, problems with colour vision, peripheral vision. There are no statistically significant differences.
j. Includes events of the underlying disease; in the present data basis, however, the analyses are usable, as it is assumed that the disease-related events included in the respective evaluation have no relevant impact on the study results.
k. Including endophthalmitis and retinal vascular occlusion; operationalised as ocular AESI.
l. Refers to the eye under study.
m. Including endophthalmitis and retinal vascular occlusion; operationalised as ocular SAEs.

Abbreviations used:
ANCOVA = Analysis of Covariance; CTCAE = Common Terminology Criteria for Adverse Events; ETDRS = Early Treatment Diabetic Retinopathy Study; n.d. = no data available; CI = confidence interval; MD = mean difference; MV = mean value; N = number of patients analysed; n = number of patients with (at least one) event; NEI VFQ-25 = National Eye Institute Function Questionnaire-25; RR = relative risk; SD = standard deviation; SAE = serious adverse event; AE = adverse event; AESI = adverse event of specific interest; vs = versus

2. Number of patients or demarcation of patient groups eligible for treatment

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

approx. 85,200 – 681,400 patients

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 Beovu 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.

4. Treatment costs

Annual treatment costs:

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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Brolucizumab	1st year: € 4,644.80 - € 7,431.68
	Subsequent years: € 3,994.53 - € 6,038.24
Intravitreal injection	1st year: € 464.25 - € 1,589.60
	Subsequent years: € 399.26 - € 1,291.55
Postoperative treatment	1st year: € 99.65 - € 222.48
	Subsequent years: € 85.70 - € 180.77
Additionally required SHI services	non-quantifiable[2]
Total	1st year: € 5,208.70 - € 9,243.76
	Subsequent years: € 4,479.48 - € 7,510.56
Appropriate comparator therapy:	
Aflibercept	1st year: € 6,223.08 - € 7,260.26
	Subsequent years: € 0 - € 6,223.08
Intravitreal injection	1st year: € 557.10 - € 1,390.90
	Subsequent years: € 0 - € 1,192.20
Postoperative treatment	1st year: € 119.58 - € 194.67
	Subsequent years: € 0 - € 166.86
Additionally required SHI services	non-quantifiable[2]
Total	1st year: € 6899.76 - € 8845.83
	Subsequent years: € 0 - € 7,582.14
Faricimab	1st year: € 5788.62 - € 8682.93
	Subsequent years: € 3183.74 - € 6271.01
Intravitreal injection	1st year: € 557.10 - € 1788.30

2 Due to the patient-individual determination of the type and frequency of check-ups by the attending physician, the costs incurred for additionally required SHI services, such as further check-ups or, e.g. optical coherence tomography are non-quantifiable.

Designation of the therapy	Annual treatment costs/ patient
	Subsequent years: € 306.41 - € 1291.55
Postoperative treatment	1st year: € 119.58 - € 250.29
	Subsequent years: € 65.77 - € 180.77
Additionally required SHI services	non-quantifiable[2]
Total	1st year: € 6,465.30 - € 1,0721.52
	Subsequent years: € 3,555.92 - € 7,743.32
Ranibizumab	1st year: € 6,753.39 - € 11,577.24
	Subsequent years: € 0 -€ 11,577.24
Intravitreal injection	1st year: € 649.95 - € 2,384.40
	Subsequent years: € 0 - € 2,384.40
Postoperative treatment	1st year: € 139.51 - € 333.72
	Subsequent years: € 0 - € 333.72
Additionally required SHI services	non-quantifiable[2]
Total	1st year: € 7,542.85 - € 14,295.36
	Subsequent years: € 0 - € 14,295.36

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 April 2024

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

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

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

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

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. 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.

III. The resolution will enter into force on the day of its publication on the website of the G-BA on 2 May 2024.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 2 May 2024

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

Prof. Hecken