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 and Annex XIIa – Combinations of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Benralizumab (new therapeutic indication: eosinophilic granulomatosis with polyangiitis)

of 15 May 2025

At their session on 15 May 2025, 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. In Annex XII, the following information shall be added after No. 5 to the information on the benefit assessment of Benralizumab in accordance with the resolution of 2 August 2018.**

**Benralizumab**

Resolution of: 15 May 2025
Entry into force on: 15 May 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

**New therapeutic indication (according to the marketing authorisation of 24 October 2024):**

Fasenra is indicated as an add-on treatment for adult patients with relapsing or refractory eosinophilic granulomatosis with polyangiitis.

**Therapeutic indication of the resolution (resolution of 15 May 2025):**

See new therapeutic indication according to marketing authorisation.

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

a) Adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis **with** organ-threatening or life-threatening manifestations; for add-on treatment

**Appropriate comparator therapy for benralizumab as add-on treatment:**

- Individualised therapy with selection of cyclophosphamide and rituximab for remission induction followed by mepolizumab for remission maintenance, each in combination with glucocorticoids

**Extent and probability of the additional benefit of benralizumab compared to the appropriate comparator therapy:**

An additional benefit is not proven.

b) Adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis **without** organ-threatening or life-threatening manifestations; for add-on treatment

**Appropriate comparator therapy for benralizumab as add-on treatment:**

- Mepolizumab

**Extent and probability of the additional benefit of benralizumab compared to mepolizumab:**

An additional benefit is not proven.

**Study results according to endpoints:**[1]

[1] Data from the dossier assessment of the IQWiG (A24-113) and from the addendum (A25-49), unless otherwise indicated.

a) Adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis **with** organ-threatening or life-threatening manifestations; for add-on treatment

No data available.

**Summary of results for relevant clinical endpoints**

| Endpoint category | Direction of effect/ risk of bias | Summary |
|---|---|---|
| Mortality | ∅ | No data available. |
| Morbidity | ∅ | No data available. |
| Health-related quality of life | ∅ | No data available. |
| Side effects | ∅ | No data available. |

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

b) Adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis **without** organ-threatening or life-threatening manifestations; for add-on treatment

**Summary of results for relevant clinical endpoints**

| Endpoint category | Direction of effect/ risk of bias | Summary |
|---|---|---|
| Mortality | ↔ | No deaths occurred. |
| Morbidity | ↔ | No relevant differences for the benefit assessment. |
| Health-related quality of life | ↔ | No relevant differences for the benefit assessment in SF-36. |
| Side effects | ↔ | No relevant differences for the benefit assessment. |

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

MANDARA study: Randomised controlled trial over 52 weeks, benralizumab versus mepolizumab each as add-on treatment to oral corticosteroids +/- immunosuppressant (basic therapy)

**Mortality**

| Endpoint | Benralizumab + basic therapy | | Mepolizumab + basic therapy | | Benralizumab versus mepolizumab |
|---|---|---|---|---|---|
| | *N* | *Patients with event n (%)* | *N* | *Patients with event n (%)* | *RR [95 % CI]; p-value*[a] |
| **Overall mortality**[b] (within 52 weeks) | | | | | |
| | 70 | 0 (0) | 70 | 0 (0) | -- |

**Morbidity**

| Endpoint | Benralizumab + basic therapy | | Mepolizumab + basic therapy | | Benralizumab versus mepolizumab |
|---|---|---|---|---|---|
| | *N* | *Patients with event n (%)* | *N* | *Patients with event n (%)* | *RR [95 % CI]; p-value*[a] |
| **Remission** (BVAS = 0 and OCS ≤ 7.5 mg/day; within the first 24 weeks until week 52) | | | | | |
| | 70 | 41 (58.6) | 70 | 40 (57.1) | 1.12 [0.89; 1.40]; 0.336[c] |
| **Absence of vasculitis disease activity** (BVAS = 0; within the first 24 weeks until week 52) (presented additionally) | | | | | |
| | 70 | 42 (60.0) | 70 | 44 (62.9) | 0.96 [0.73; 1.25]; 0.743[c] |
| **Severe EGPA symptomatology** | | | | | |
| | No suitable data | | | | |
| **Asthma symptomatology** (ACQ-6, improvement averaged over weeks 49 to 52)[d] | | | | | |
| | 70 | 24 (34.3) | 70 | 20 (28.6) | 1.20 [0.73; 1.96]; 0.531 |
| **Sinonasal symptomatology** (SNOT-22, improvement at week 52)[e] | | | | | |
| | 70 | 18 (25.7) | 70 | 13 (18.6) | 1.39 [0.74; 2.60]; 0.338 |
| **Activity impairment** (WPAI question 6, improvement at week 52)[f] | | | | | |
| | 70 | 22 (31.4) | 70 | 20 (28.6) | 1.10 [0.66; 1.83]; 0.792 |
| **Symptomatology** (PGIS, improvement at week 52)[g] | | | | | |

| Endpoint | Benralizumab + basic therapy | | Mepolizumab + basic therapy | | Benralizumab versus mepolizumab |
|---|---|---|---|---|---|
| | *N* | *Patients with event n (%)* | *N* | *Patients with event n (%)* | *RR [95 % CI]; p-value[a]* |
| | 70 | 26 (37.1) | 70 | 33 (47.1) | 0.79 [0.53; 1.17]; 0.250 |
| **Endpoint** | **Benralizumab + basic therapy** | | **Mepolizumab + basic therapy** | | **Benralizumab versus mepolizumab** |
| | *N* | *Number of events annual rate [95% CI]* | *N* | *Number of events annual rate [95% CI]* | *Rate ratio [95% CI]; p value[i]* |
| **Relapse**[i] (deterioration or persistence of the active disease since the last visit) (presented additionally) | | | | | |
| | 70 | 34<br>0.48 [n.d.] | 70 | 30<br>0.43 [n.d.] | 1.03 [0.56; 1.90]; 0.928 |

**Health-related quality of life**

| Endpoint | Benralizumab + basic therapy | | Mepolizumab + basic therapy | | Benralizumab versus mepolizumab |
|---|---|---|---|---|---|
| | *N* | *Patients with event n (%)* | *N* | *Patients with event n (%)* | *RR [95 % CI]; p-value[a]* |
| **SF-36v2** (improvement at week 52)[j] | | | | | |
| Physical Component Summary (PCS) score | 70 | 7 (10.0) | 70 | 8 (11.4) | 0.88 [0.34; 2.28]; 0.862 |
| Mental Component Summary (MCS) score | 70 | 10 (14.3) | 70 | 12 (17.1) | 0.83 [0.39; 1.80]; 0.687 |

**Side effects**

| Endpoint | Benralizumab + basic therapy | | Mepolizumab + basic therapy | | Benralizumab versus mepolizumab |
|---|---|---|---|---|---|
| | *N* | *Patients with event n (%)* | *N* | *Patients with event n (%)* | *RR [95 % CI]; p-value[a]* |
| **Total adverse events** (presented additionally) | | | | | |
| | 70 | 63 (90.0) | 70 | 67 (95.7) | – |
| **Serious adverse events (SAE)** | | | | | |
| | 70 | 4 (5.7) | 70 | 9 (12.9) | 0.44 [0.14; 1.38]; 0.167 |
| **Therapy discontinuation due to adverse events** | | | | | |
| | 70 | 0 (0) | 70 | 2 (2.9) | 0.20 [0.01; 4.09]; 0.210 |

a RR unadjusted, p value: IQWiG calculation
b Fatalities were collected as part of AEs
c RR, 95% CI and p value are based on a log-binomial regression with treatment group, baseline BVAS (BVAS = 0 vs BVAS > 0) and baseline OCS dose (< 12 mg/day vs ≥ 12 mg/day) as factors.
d A mean decrease in ACQ-6 score by ≥ 0.9 points in the weeks 49-52 compared to the start of the study is considered a clinically relevant improvement (scale range 0 to 6).
e A decrease in SNOT-22 total score by ≥ 16.5 points at week 52 compared to the start of the study is considered a clinically relevant improvement (scale range 0 to 110).
f A decrease in WPAI score (question 6) by ≥ 15 points at week 52 compared to the start of the study is considered a clinically relevant improvement (scale range 0 to 100).
g A decrease by ≥ 1 point compared to the start of the study is considered a clinically relevant improvement (scale range from 0 "no symptoms" to 5 "very severe").
h Rate ratio including CI and p value is based on a negative-binomial model with treatment group, OCS dose at baseline, BVAS at baseline, region and logarithmised treatment duration (offset variable)
i Patients with at least 1 relapse: 21 (intervention) vs 21 (control) An increase in the
j PCS score by ≥ 9.4 points or MCS score by ≥ 9.6 points at week 52 compared to the start of the study is considered a clinically relevant improvement (scale range: 10.8 to 75.5 for PCS and 5.6 to 69.7 for MCS).

Abbreviations used:
ACQ: Asthma Control Questionnaire; BVAS: Birmingham Vasculitis Activity Score; EGPA: eosinophilic granulomatosis with polyangiitis; n.d.: no data available; CI: confidence Interval; MCS: Mental Component Summary; n: number of patients with (at least 1) event; N: number of patients evaluated; n.r. = not reached; OCS: oral glucocorticoids; PCS: Physical Component Summary; PGIS: Patient Global Impression of Severity, PC: pharmaceutical company, RCT: randomised controlled trial, RR: relative risk, SF-36v2: Short Form 36-item health survey version 2; SNOT-22: 22-item Sino-Nasal Outcome Test; SAE: serious adverse event; AE: adverse event; WPAI: Work Productivity and Activity Impairment

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

a) Adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis **with** organ-threatening or life-threatening manifestations; for add-on treatment

and

b) Adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis without organ-threatening or life-threatening manifestations; for add-on treatment

Approx. 90 – 1,360 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 Fasenra (active ingredient: benralizumab) at the following publicly accessible link (last access: 5 March 2025):

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

Treatment with benralizumab should only be initiated and monitored by doctors experienced in the therapy of EGPA.

Benralizumab is intended for long-term treatment. A decision on the continuation of therapy should be made at least once a year. Patients who develop life-threatening manifestations of EGPA should be assessed for the need for continued therapy as Fasenra has not been studied in this patient group.

## 4. Treatment costs

**Annual treatment costs:**

a) Adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis **with** organ-threatening or life-threatening manifestations; for add-on treatment

| Designation of the therapy | Annual treatment costs/ patient |
|---|---|
| Medicinal product to be assessed: | |
| Benralizumab | € 31,966.35 |
| Prednisolone | Different from patient to patient |
| Appropriate comparator therapy: | |
| Individualised therapy with selection of cyclophosphamide and rituximab for remission induction followed by mepolizumab for remission maintenance, each in combination with glucocorticoids | |
| Cyclophosphamide followed by | € 25,654.16 – € 33,769.71 |

| Designation of the therapy | Annual treatment costs/ patient |
|---|---|
| mepolizumab | |
| Cyclophosphamide[2] | € 198.36 – € 289.14 |
| Mepolizumab | € 25,365.02 – € 33,571.35 |
| Prednisolone | Different from patient to patient |
| Rituximab followed by mepolizumab | € 27,595.75 |
| Rituximab | € 2,976.76 |
| Mepolizumab | € 24,618.99 |
| Prednisolone | Different from patient to patient |

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 April 2025)

b) Adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis **without** organ-threatening or life-threatening manifestations; for add-on treatment

| Designation of the therapy | Annual treatment costs/ patient |
|---|---|
| Medicinal product to be assessed: | |
| Benralizumab | € 31,966.35 |
| Prednisolone | Different from patient to patient |
| Appropriate comparator therapy: | |
| Mepolizumab | € 48,491.95 |
| Prednisolone | Different from patient to patient |

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 April 2025)

Costs for additionally required SHI services: not applicable

[2] Entire medicinal product packages (N1, N2 and N3) were used to calculate the treatment costs.

Other SHI services:

| Designation of the therapy | Type of service | Costs/ unit | Number/ cycle | Number/ patient/ year | Costs/ patient/ year |
|---|---|---|---|---|---|
| Cyclophosphamide | Surcharge for production of a parenteral preparation containing cytostatic agents | € 100 | 1 | 6 - 9 | € 600 – € 900 |
| Rituximab | Surcharge for the preparation of a parenteral solution containing monoclonal antibodies | € 100 | 1 | 2 | € 200 |

## 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:

a) Adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis **with** organ-threatening or life-threatening manifestations; for add-on treatment

The following medicinal products with new active ingredients that can be used in a combination therapy with benralizumab in the therapeutic indication of the resolution on the basis of the marketing authorisation under Medicinal Products Act are named (active ingredients and invented names) in accordance with Section 35a, paragraph 3, sentence 4 SGB V:

– Mepolizumab (Nucala)

b) Adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis **without** organ-threatening or life-threatening manifestations; for add-on treatment

The following medicinal products with new active ingredients that can be used in a combination therapy with benralizumab in the therapeutic indication of the resolution on the basis of the marketing authorisation under Medicinal Products Act are named (active ingredients and invented names) in accordance with Section 35a, paragraph 3, sentence 4 SGB V:

– Mepolizumab (Nucala)

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.

II. **In Annex XIIa of the Pharmaceuticals Directive, the following information shall be added in alphabetical order:**

Active ingredient of the assessed medicinal product

Benralizumab

Resolution according to Section 35a paragraph 3 SGB V from

15 May 2025

Therapeutic indication of the resolution

Fasenra is indicated as an add-on treatment for adult patients with relapsing or refractory eosinophilic granulomatosis with polyangiitis.

Patient group a

Adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis **with** organ-threatening or life-threatening manifestations; for add-on treatment

Naming of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V (active ingredients and invented names[2])
Mepolizumab (Nucala)

Period of validity of the designation (since... or from... to)

Since 15 May 2025

Patient group b

Adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis **without** organ-threatening or life-threatening manifestations; for add-on treatment

Naming of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V (active ingredients and invented names[2])
Mepolizumab (Nucala)

Period of validity of the designation (since... or from... to)

Since 15 May 2025

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 15 May 2025.**

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

Berlin, 15 May 2025

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

Prof. Hecken