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 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

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 all reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient benralizumab (Fasenra) was listed for the first time on 15 February 2018 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 24 October 2024, benralizumab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 21 November 2024, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient benralizumab with

the new therapeutic indication "Fasenra is indicated as an add-on treatment for adult patients with relapsing or refractory eosinophilic granulomatosis with polyangiitis" in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 21 November 2024 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of benralizumab compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, as well of the addendum drawn up by the IQWiG on the benefit assessment. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of benralizumab.

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 Benralizumab (Fasenra) in accordance with the product information

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 15.05.2025):

See the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Appropriate comparator therapy for benralizumab as add-on treatment:

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

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

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

Appropriate comparator therapy for benralizumab as add-on treatment:

- Mepolizumab

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

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application, unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

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

3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

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

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

On 1. In addition to the active ingredient to be assessed, mepolizumab and systemic corticosteroids (prednisolone, prednisone and methylprednisone) are approved in the planned therapeutic indication.

On 2. Plasmapheresis can be considered as a non-medicinal treatment.

On 3. A resolution of 19 May 2022 on the benefit assessment of mepolizumab according to Section 35a SGB V is available.

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present 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.

The reliable evidence in the present therapeutic indication is limited overall. Three guidelines - an American guideline[2], an evidence-based guideline from a European expert panel[3] and the current recommendations of the European Alliance of Associations for Rheumatology (EULAR)[4] - as well as a systematic review were identified. In addition, the German S3 guideline "Diagnostics and therapy of ANCA-associated vasculitis"[5] was published in 2024.

The therapy recommendations of the mentioned guidelines essentially depend on the severity grade of the disease, i.e. whether an organ-threatening or life-threatening stage of the disease is present or not. A division into the following two patient groups is therefore considered appropriate:

[2] Chung SA, et al. 2021 American College of Rheumatology/Vasculitis Foundation guideline for the management of antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheumatol 2021;73(8):1366-1383.
[3] Emmi G, et al. Evidence-based guideline for the diagnosis and management of eosinophilic granulomatosis with polyangiitis. Nat Rev Rheumatol 2023;19(6):378-393.
[4] Hellmich B, et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. Ann Rheum Dis 2023 [Online ahead of print]. https://ard.bmj.com/content/annrheumdis/early/2023/03/16/ard-2022-223764.full.pdf
[5] Holle JU, et al. S3 guideline - Diagnostics and therapy of ANCA-associated vasculitis. 2024. [last revised 11.03.2025] https://register.awmf.org/de/leitlinien/detail/060-012

a) Adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis **with** organ-threatening or ~~life-threatening symptom~~life-threatening manifestations

and

b) adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis **without** organ-threatening or ~~life-threatening symptom~~life-threatening manifestations

On a)

The treatment of EGPA **with** organ-threatening or ~~life-threatening symptom~~life-threatening manifestations is divided into two treatment phases: The initial treatment for remission induction and the subsequent remission maintenance treatment.

Remission induction

In an organ-threatening or life-threatening manifestation of the disease, high doses of oral glucocorticoids are usually used to induce remission. If necessary, oral therapy is preceded by intravenous pulse therapy with glucocorticoids. In addition to glucocorticoids, the guidelines recommend the use of cyclophosphamide or, alternatively, rituximab for the induction of remission in the event of a relapse with organ-threatening or ~~life-threatening symptom~~life-threatening manifestations. Also from the point of view of the scientific-medical societies, cyclophosphamide as an add-on treatment to glucocorticoids - with reference to the EULAR guideline - is the standard therapy for remission induction in relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA) with organ-threatening or ~~life-threatening symptom~~life-threatening manifestations. Rituximab is mentioned as an alternative. Refractory EGPA patients with organ- or ~~life-threatening symptom~~life-threatening manifestations~~s~~ should be switched from cyclophosphamide to rituximab, or from rituximab to cyclophosphamide.

According to the S3 guideline, additional plasma exchange should not be performed.

The available body of evidence for this specific study setting in this generally rare disease is very limited.

The recommended active ingredients cyclophosphamide and rituximab are not approved for the treatment of EGPA. Glucocorticoids and mepolizumab (as an adjunctive treatment for relapsing or refractory EGPA) are approved active ingredients in this therapeutic indication. As already described, glucocorticoids are generally used as a combination therapy in patients with organ-threatening or ~~life-threatening symptom~~life-threatening manifestations of EGPA, and are therefore not considered as the sole therapy.

The approved therapeutic indication for mepolizumab covers all severity grades. However, the product information points out that mepolizumab has not been studied in subjects with organ-threatening or ~~life-threatening symptom~~life-threatening manifestations of EGPA. Furthermore, mepolizumab is not considered a standard therapy for the induction of remission in this patient population as mepolizumab is not recommended in the guidelines for the induction of remission in this severe manifestation of the disease.

Consequently, the off-label use of cyclophosphamide and rituximab as an adjuvant treatment to glucocorticoids for remission induction is medically necessary and, according to the generally recognised state of medical knowledge, is considered the therapy standard in adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA) with organ-threatening or ~~life-threatening symptom~~life-threatening manifestations, and is usually preferable to the medicinal product mepolizumab, which has previously been approved in this therapeutic indication (Section 6, paragraph 2, sentence 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV)). Therefore, it is appropriate to determine the off-label use of cyclophosphamide and rituximab as the appropriate comparator therapy.

Remission maintenance

Oral glucocorticoids continue to be used in remission maintenance treatment. However, the aim is to keep the dosage as low as possible in order to avoid side effects.

Glucocorticoid-sparing combination therapy should therefore be used for remission maintenance. In subjects with an organ-threatening or ~~life-threatening symptom~~life-threatening manifestations (after new-onset or relapse), treatment with conventional non-steroidal immunosuppressants, mepolizumab or rituximab should be considered in accordance with the mentioned guidelines and the assessment of the scientific-medical societies. However, rituximab and conventional non-steroidal immunosuppressants are not approved for this therapeutic indication. In view of the availability of the approved active ingredient mepolizumab recommended by the guidelines, the available evidence does not indicate a compelling medical need for these active ingredient options. Thus, only mepolizumab is considered as an appropriate comparator therapy for remission maintenance in organ-threatening or ~~life-threatening symptom~~life-threatening manifestations of EGPA.

In the overall assessment, an individualised treatment with selection of cyclophosphamide and rituximab for remission induction followed by mepolizumab for remission maintenance, in each case in combination with glucocorticoids, is determined as the appropriate comparator therapy for adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA) with organ-threatening or ~~life-threatening symptom~~life-threatening manifestations.

Individualised therapy is based on the assumption that several treatment options, which allow an individualised medical treatment decision, are available.

Editorial note: The term "individualised therapy" is used instead of previously used terms such as "patient-individual therapy" or "therapy according to doctor's instructions". This harmonises the terms used in the European assessment procedures (EU-HTA).

On b)

The use of mepolizumab as an add-on treatment to a basic therapy with glucocorticoids is primarily recommended for the treatment of patients with EGPA without organ-damaging or ~~life-threatening symptom~~life-threatening manifestations, who have suffered relapses or who have not achieved remission despite remission induction treatment. Mepolizumab should be used in both treatment phases, i.e. both for induction and maintenance of remission.

The sole administration of glucocorticoids may also be an option for some patients with EGPA without organ-damaging or ~~life-threatening symptom~~life-threatening manifestations. However, it is assumed that patients in this therapeutic indication are ineligible for treatment with glucocorticoids alone as they are eligible for treatment with benralizumab as an add-on treatment.

In the overall assessment, the active ingredient mepolizumab was determined as an appropriate comparator therapy for adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis without organ-threatening or ~~life-threatening symptom~~life-threatening manifestations. As a basic therapy, glucocorticoids are usually indicated in line with the guidelines.

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

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

2.1.3 Extent and probability of the additional benefit

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

a) For adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis **with** organ-threatening or ~~life-threatening symptom~~life-threatening manifestations; for add-on treatment, an additional benefit is not proven.

b) For adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis **without** organ-threatening or ~~life-threatening symptom~~life-threatening manifestations; for add-on treatment, an additional benefit is not proven.

Justification:

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

The pharmaceutical company did not submit any studies on the add-on treatment of adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA) with organ-threatening or ~~life-threatening symptom~~life-threatening manifestations, compared with the appropriate comparator therapy.

An additional benefit of benralizumab over the appropriate comparator therapy is therefore not proven for the add-on treatment of adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA) with organ-threatening or ~~life-threatening symptom~~life-threatening manifestations.

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

The pharmaceutical company presented the MANDARA study on the add-on treatment of adults with relapsing or refractory EGPA without organ-threatening or ~~life-threatening symptom~~life-threatening manifestations. This study comprises a double-blind, randomised controlled trial phase comparing benralizumab with mepolizumab in adults with EGPA over 52 weeks, followed by a single-arm, open-label extension phase with benralizumab for at least 1 year. The extension phase is not considered for the present benefit assessment due to the lack of comparison.

EGPA had to have been diagnosed in the study participants at least 6 months before screening - based on the medical history or the presence of asthma and eosinophilia as well as at least 2 other EGPA characteristics. Patients with active disease as well as those with a history of relapsing or refractory disease were enrolled. 49% of patients in the intervention arm and 47% in the comparator arm had active disease at the start of the study (Birmingham Vasculitis Activity Score (BVAS) > 0). Patients with organ-threatening or life-threatening EGPA were excluded from study participation.

A total of 140 patients were randomised in a 1:1 ratio to a 52-week treatment with benralizumab (N = 70) or mepolizumab (N = 70). In addition to the respective biologic agent, patients in both study arms received a basic therapy consisting of oral glucocorticoids (oral corticosteroids, OCS) and, if necessary, immunosuppressants.

The dosage of OCS (prednisolone or equivalent) had to be stable at a minimum of 7.5 mg/day to a maximum of 50 mg/day at the time of enrolment in the study. From study week 4 onwards, in the absence of disease activity (BVAS = 0) or at the doctor's discretion, the dose should be reduced in accordance with standard treatment practice. Immunosuppressants (e.g. azathioprine, methotrexate, mycophenolate mofetil) could only be used if the dosage was kept stable for at least 4 weeks before the start of the study until the end of the study. Cyclophosphamide and rituximab were not permitted in the study.

The primary endpoint of the MANDARA study is the percentage of patients who are in remission at both week 36 and week 48. Other patient-relevant endpoints were assessed in the categories of morbidity, health-related quality of life and side effects.

Extent and probability of the additional benefit

Mortality

Overall survival

No deaths occurred during the 52-week double-blind phase of the MANDARA study.

Morbidity

Remission

Both remission and maintenance of remission are central therapeutic goals in the present therapeutic indication and of high clinical relevance.

In the dossier and in the course of the written statement procedure, the pharmaceutical company submitted several operationalisations with different definitions and evaluation times of the endpoint.

Remission was defined as the absence of any disease activity (BVAS = 0) and the achievement of a specific OCS dose threshold value of either ≤ 7.5 mg/day, ≤ 4 mg/day or 0 mg/day (steroid-free remission).

The definition of remission with the OCS dose threshold value ≤ 7.5 mg/day in the MANDARA study was a supportive analysis for the primary endpoint of remission (BVAS = 0 and OCS dose ≤ 4 mg/day). In the present benefit assessment, this pre-specified definition is used in view of the recommendation of the current S3 guideline with the daily OCS dose threshold value of 7.5 mg.

According to EULAR, the probability of relapse is particularly high within the first 6 months of remission. For this reason, the evaluation of the percentage of patients who achieve a remission within the first 24 weeks and remain in remission until the end of the study (week 52, i.e. at least 28 weeks) is considered in this benefit assessment.

The BVAS is an instrument for measuring disease activity in subjects with systemic vasculitis, which is completed by medical staff. The BVAS is divided into 9 organ-based systems, with each section containing symptoms or signs that are typical of the involvement of the respective organ in systemic vasculitis. Although the BVAS also includes items whose assessment is based on imaging and laboratory parameters that are not per se patient-relevant when considered individually, the absence of any disease activity (BVAS = 0) is considered patient-relevant. However, the EGPA symptoms of asthma and sinonasal symptomatology may not be comprehensively covered as the BVAS was not developed specifically for the EGPA indication.

There was no statistically significant difference between the treatment groups for the endpoint of remission within the first 24 weeks up to week 52 with the OCS threshold value of 7.5 mg/day. The individual component of no disease activity (BVAS = 0) is presented additionally.

The "steroid-free remission" endpoint is not used for the assessment of the additional benefit in the present resolution, as there are fundamental uncertainties as to whether the time periods presented by the pharmaceutical company are appropriate for the "steroid-free remission" endpoint. The endpoint should generally be achievable for almost all patients for an appropriate evaluation of steroid-free remission. However, based on the time points presented, it remains unclear whether a relevant percentage of the enrolled patients did not have the opportunity to achieve a steroid-free remission at the selected time points (with the possible exception of the evaluation at week 52). The evaluation period should also be selected in such a way that potential effects cannot be caused solely by patients in one treatment arm achieving the endpoint just a few weeks earlier.

Furthermore, heterogeneous results are observed for the various evaluations. Only some of the evaluations presented showed a statistically significant difference between the treatment arms. The evaluations of steroid-free remission at week 36 with maintenance until week 48 and at week 36 with maintenance until week 52 each showed a statistically significant effect to the advantage of benralizumab. However, the evaluation of steroid-free remission at the end of the study at week 52 showed no statistically significant difference between benralizumab and mepolizumab, although the percentage of remission was significantly higher in absolute terms. Likewise, the evaluation of steroid-free remission at week 24 with maintenance until week 52 showed no statistically significant difference between the

treatment arms. It remains unclear to what extent the uncertainties at the different survey periods and time points influence the results.

Relapse

In the MANDARA study, the endpoint of relapse is defined as deterioration or persistence of active disease since the last visit. Deterioration or persistence of active disease is characterised by the presence of vasculitis (BVAS > 0) or asthma symptoms and/or signs with deterioration of the ACQ-6 score (see below) or nasal and/or sinus disease with deterioration of at least one symptom of the sinonasal symptomatology assessment questionnaire.

In addition, the following requirements must be met:
- increase of the OCS dose to > 4 mg/day or
- increase in dose or additional immunosuppressive therapy or
- hospitalisation due to deterioration of EGPA.

At the start of the study, 51% of patients in the intervention arm and 53% in the control arm had a BVAS = 0. In accordance with the inclusion criteria, patients with a daily OCS dose of at least 7.5 mg were enrolled in the study. The number of patients who were in remission at the start of the study according to the S3 guideline definition (BVAS = 0 and OCS dose ≤ 7.5 mg/day) remains unclear. However, achieving and maintaining remission is considered the primarily relevant evaluation in the present setting. If remission and relapse were considered simultaneously in accordance with the operationalisations described, a double counting of patients could not be ruled out when considering one survey time point. This means that subjects can be categorised as being in remission and relapsing at the same time. In the overall assessment, the "relapse" endpoint is only considered additionally and not taken into account for the derivation of the additional benefit.

For the endpoint of relapse (annual rate), there were no statistically significant differences between benralizumab and mepolizumab.

Average OCS dose (reduction) and steroid avoidance

For the endpoint of OCS dose (reduction), the pharmaceutical company presented various continuous evaluations for comparison at the start of the study as well as responder analyses on the percentage of patients with an average daily OCS dose of 0 mg/day (steroid avoidance), ≤ 4 mg/day and ≤ 7.5 mg/day at weeks 49 to 52. For the present benefit assessment, the average OCS dose (reduction) including steroid avoidance is not used, as the OCS dose should be considered appropriately in the remission definition.

Severe EGPA symptomatology

The pharmaceutical company operationalised the endpoint "severe EGPA symptomatology" as EGPA-associated hospitalisation and submitted the percentage of patients with EGPA-associated hospitalisation and the annual hospitalisation rate up to week 52 in the dossier. The results for severe EGPA symptomatology were not presented, as it is unclear whether the results presented are EGPA-associated hospitalisations or hospitalisations due to adverse events (AEs). The ambiguity could not be resolved by the subsequently submitted information on the disease-related AEs taken into account.

Asthma symptomatology (assessed using ACQ-6)

Asthma control was assessed using the standardised *Asthma Control Questionnaire* (ACQ). This contains 7 questions and a summary score between 0 (= no symptoms) and 6 (= no asthma control). The cut-off value for a patient not being well controlled is ≥ 1. The reduced version of the ACQ-6 does not include the question regarding the FEV1 value. In addition to 5 questions on symptomatology, the total score of the ACQ-6 includes 1 question related to on-demand medication.

In the present benefit assessment, the percentage of patients who showed a clinically relevant improvement, i.e. a mean decrease in the ACQ-6 score by ≥ 0.9 points, in weeks 49 to 52 compared to the start of the study is considered.

For the endpoint of asthma symptomatology (assessed using ACQ-6), there was no statistically significant difference between the treatment groups.

Sinonasal symptomatology (assessed using SNOT-22)

In the MANDARA study, sinonasal symptomatology was assessed using the *22-item Sino-Nasal Outcome Test* (SNOT-22). This is a disease-specific, patient-reported questionnaire to assess the severity and frequency of symptoms and social/ emotional consequences of rhinosinusitis. Each question is answered on a scale from 0 (no complaints) to 5 (worst possible complaints) and a total score (0 to 110) is calculated from the individual scores for each question, with lower values corresponding to less impairment.

In the present benefit assessment, the percentage of patients who showed a clinically relevant improvement, i.e. a decrease in the SNOT-22 total score by ≥ 16.5 points, at week 52 compared to the start of the study is considered.

For the endpoint of sinonasal symptomatology, there was no statistically significant difference between the treatment groups.

Activity impairment (assessed using WPAI question 6)

The *Work Productivity and Activity Impairment* (WPAI) is used to collect impairments to work productivity and activities. Health economic aspects such as the endpoints of absenteeism and presenteeism collected by the WPAI are not considered patient-relevant and are therefore not taken into account in this benefit assessment. However, activity impairment due to the disease (question 6) addresses a patient-relevant aspect.

The present benefit assessment is therefore based on the percentage of patients who showed a clinically relevant improvement in activity impairment, i.e. a decrease in the WPAI score (question 6) by ≥ 15 points at week 52 compared to the start of the study.

For the endpoint of activity impairment, there was no statistically significant difference between the treatment groups.

Symptomatology (assessed using PGIS)

Symptomatology was assessed in the MANDARA study using the *Patient Global Impression of Severity* (PGIS). The value range of the patient-reported 1-item scale extends from 0 "no symptoms" to 5 "very severe". The responder analyses at week 52 are used for the present

benefit assessment. A decrease by ≥ 1 point compared to the start of the study is considered a clinically relevant improvement.

There was no significant difference between the treatment arms. When interpreting the results, it should however be noted that a high percentage (> 10%) of the values were replaced by non-responder imputation.

Vasculitic organ damage (assessed using VDI)

In the dossier, the pharmaceutical company presented results on the endpoint of vasculitic organ damage assessed using the Vasculitis Damage Index (VDI). The VDI is a doctor-reported instrument for measuring organ damage in subjects with systemic vasculitis. The organ damage is determined on the basis of 64 items, divided into 11 organ system categories. Damage is defined as the existence of a medical event over a period of ≥ 3 months after the onset of vasculitis. One point is awarded for each item of the VDI if damage is detected, so that a total score of 0 points (no damage) to a maximum of 64 points can be achieved. The VDI assesses organ damage cumulatively, so that the score can only remain stable or increase over time, but not decrease. A health impairment that has subsided over time is still included in the total score of subsequent assessments.

Organ damage is considered patient-relevant. However, the assessment of organ damage using the VDI is partly based on vital parameters, imaging procedures and laboratory parameters and not exclusively on symptomatology perceivable by patients. The VDI also collects events of varying severity grades.

For the assessment of organ damage using VDI, it therefore remains unclear whether all events collected are patient-relevant and to what extent events of varying severity grades were included in the score. Furthermore, it remains unclear whether some of the collected events are reversible and therefore do not represent permanent organ damage. For these reasons, the VDI is not used for the present benefit assessment.

Quality of life

Health-related quality of life (assessed using SF-36v2)

In the MANDARA study, health-related quality of life was assessed using the acute version of the generic Short Form 36-item health survey version 2 (SF-36v2) questionnaire.

The results were evaluated as a responder analysis, whereby the study participants who showed an increase in the Physical Component Summary (PCS) score by ≥ 9.4 points or Mental Component Summary (MCS) score by ≥ 9.6 points at week 52 compared to the start of the study were counted as responders. The response thresholds used were determined on the basis of the value range of the standard Sf-36v2 version. However, in the acute SF-36v2 version used in the present study, the response threshold for the PCS differs slightly from the standard version.

There was no statistically significant difference between the treatment groups for the endpoint of health-related quality of life (assessed using SF-36v2) for either the PCS or the MCS.

Side effects

For the endpoints of serious adverse events (AE) and discontinuation due to AEs, there was no statistically significant difference between the treatment groups in each case.

Overall assessment

For the add-on treatment of adults with relapsing or refractory EGPA without organ-threatening or ~~life-threatening symptom~~life-threatening manifestations, the results of the MANDARA study comparing the efficacy and safety of benralizumab with mepolizumab over 52 weeks are available.

There were no deaths in this study.

In the morbidity category, there were neither advantages nor disadvantages of benralizumab over mepolizumab for the endpoints of remission, asthma symptomatology (using ACQ-6), sinonasal symptomatology (using SNOT-22), activity impairment (using WPAI question 6) and symptomatology (using PGIS).

There were also no statistically significant differences between benralizumab and mepolizumab in the category of health-related quality of life assessed using the generic SF-36 questionnaire and in the category of side effects.

In the overall assessment, there were neither advantages nor disadvantages of benralizumab compared with the appropriate comparator therapy of mepolizumab. For add-on treatment of adults with relapsing or refractory EGPA without organ-threatening or ~~life-threatening symptom~~life-threatening manifestations, an additional benefit is therefore not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient benralizumab. The therapeutic indication assessed here is "Fasenra is indicated as an add-on treatment for adult patients with relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA)."

Two groups of patients were distinguished in the therapeutic indication under consideration, depending on whether there was an organ-threatening or ~~life-threatening symptom~~life-threatening manifestations of EGPA or not.

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

The G-BA determined the appropriate comparator therapy to be an individualised therapy with selection of cyclophosphamide and rituximab for remission induction followed by mepolizumab for remission maintenance, each in combination with glucocorticoids.

The pharmaceutical company did not submit any studies on the add-on treatment of adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA) with organ-threatening or ~~life-threatening symptom~~life-threatening manifestations, compared with the appropriate comparator therapy.

An additional benefit of benralizumab over the appropriate comparator therapy is therefore not proven for the add-on treatment of adults with relapsing or refractory eosinophilic

granulomatosis with polyangiitis (EGPA) with organ-threatening or ~~life-threatening symptom~~life-threatening manifestations.

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

The G-BA determined mepolizumab as the appropriate comparator therapy.

The results of the MANDARA study, which compared the efficacy and safety of benralizumab with mepolizumab over 52 weeks, are available for the benefit assessment.

There were no deaths in this study. In the morbidity category, there were neither advantages nor disadvantages of benralizumab over mepolizumab for the endpoints of remission, asthma symptomatology (using ACQ-6), sinonasal symptomatology (using SNOT-22), activity impairment (using WPAI question 6) and symptomatology (using PGIS). There were also no statistically significant differences between benralizumab and mepolizumab in the category of health-related quality of life assessed using the generic SF-36 questionnaire and in the category of side effects.
The overall assessment therefore showed neither advantages nor disadvantages of benralizumab compared with the appropriate comparator therapy of mepolizumab. For the add-on treatment of adults with relapsing or refractory EGPA without organ-threatening or ~~life-threatening symptom~~life-threatening manifestations, an additional benefit of benralizumab is thus not proven.

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

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

The resolution is based on the information on patient group b) provided by the pharmaceutical company in the dossier.

The pharmaceutical company based their calculation of patient numbers on the dossier assessment on mepolizumab (resolution of 22 May 2022) and also extrapolated the prevalence data to 2024. The uncertainties already addressed in the dossier assessment on mepolizumab therefore continue to apply. In addition, more up-to-date data is also required in view of the changed treatment setting.

Patients with organ-threatening or ~~life-threatening symptom~~life-threatening manifestations may also be included in the stated patient numbers since the routine data analysis included inpatient codes and subjects receiving cyclophosphamide treatment, and the percentage of relapsing or refractory subjects with EGPA in hospitals was also determined. Therefore, the information on patient group b) is used as the basis for the resolution for the entire target population of the therapeutic indication, even if information on the percentage of subjects with organ-threatening or ~~life-threatening symptom~~life-threatening manifestations of EGPA is not available. As part of an addendum, various alternative operationalisations for dividing up the target population were also reviewed. However, no criterion could be identified that would allow division of the patient numbers in the target population with sufficient certainty.

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 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 symptom~~life-threatening manifestations~~s~~ of EGPA should be assessed for the need for continued therapy as Fasenra has not been studied in this patient group.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 March 2025).

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 for the maximum treatment duration, if specified in the product information.

The (daily) doses recommended in the product information or in the labelled publications were used as the basis for calculation.

As it is not always possible to achieve the exact calculated dose per day with the commercially available dosage strengths, in these cases rounding up or down to the next higher or lower available dose that can be achieved with the commercially available dose potencies as well as the scalability of the respective dosage form.

Benralizumab and mepolizumab are approved as an add-on treatment. Specific information on basic therapy is not available in the respective product information. In the approval studies, mepolizumab and benralizumab were used in addition to glucocorticoids and if applicable also with immunosuppressants. In the present therapeutic indication, there is a marketing authorisation only for glucocorticoids.

The dosage of oral glucocorticoids is adjusted patient-individually in the course of treatment of EGPA and does not follow a specific standard dosage. For economic reasons, prednisolone in potencies of 5 mg and 20 mg is shown as an example for the group of oral glucocorticoids. There are also packs with a potency of 10 mg and 50 mg.

For dosages depending on body weight (bw) or body surface area (BSA), the average body measurements from the official representative statistics “Microcensus 2021 – body measurements of the population” were applied (average body height: 1.72 m; average body

weight: 77.7 kg)[6]. This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916).

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

The therapy options of the appropriate comparator therapy for remission induction - cyclophosphamide and rituximab - are not approved in the present therapeutic indication. The cost representation is based on the dosage recommendations of EULAR[7] . If there is no refractory situation, it is recommended to switch to remission-maintaining therapy after 6 boluses. The range is shown up to a use of 9 boluses since therapy-refractory patients represent a target population of the therapeutic indication[8].

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Benralizumab	1 x every 28 days	13.0	1	13.0
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	3 x every 14 days, followed by 3 - 6 x every 21 days	6.0 – 9.0	1.0	6.0 – 9.0
Mepolizumab	Followed by 1 x every 28 days	9.0 – 6.8	1.0	9.0 – 6.8
Rituximab	2 x in 180 days on day 1 and 15	2.0	1	2.0
Mepolizumab	Followed by 1 x every 28 days	6.6	1	6.6
Prednisolone	Different from patient to patient			

[6] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

[7] Hellmich B, et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. Ann Rheum Dis 2023 [Online ahead of print]. https://ard.bmj.com/content/annrheumdis/early/2023/03/16/ard-2022-223764.full.pdf

[8] Holle JU, et al. S3 guideline - Diagnostics and therapy of ANCA-associated vasculitis. 2024. [last revised 11.03.2025] https://register.awmf.org/de/leitlinien/detail/060-012

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					
Benralizumab	30 mg	30 mg	1 x 30 mg	13.0	13 x 30 mg
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	600 mg/m² BSA 1,140 mg	1,140 mg	1 x 1,000 mg + 1 x 200 mg	3.0	6 x 1,000 mg + 3 x 200 mg – 9 x 1,000 mg + 3 x 200 mg
	500 mg/m² BSA 950 mg	950 mg	1 x 1,000 mg	3.0 – 6.0	
Mepolizumab	300 mg	300 mg	3 x 100 mg	9.0 – 6.8	27 x 100 mg – 20.4 x 100 mg
Rituximab	1000 mg	1000 mg	2 x 500 mg	2.0	4 x 500 mg
Mepolizumab	300 mg	300 mg	3 x 100 mg	6.6	19.8 x 100 mg
Prednisolone	Different from patient to patient				

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

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Benralizumab	1 x every 28 days	13.0	1	13.0
Prednisolone	Different from patient to patient			
Appropriate comparator therapy				
Mepolizumab	1 x every 28 days	13	1.0	13

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Prednisolone	Different from patient to patient			

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					
Benralizumab	30 mg	30 mg	1 x 30 mg	13.0	13 x 30 mg
Prednisolone	Different from patient to patient				
Appropriate comparator therapy					
Mepolizumab	300 mg	300 mg	3 x 100 mg	13.0	39 x 100 mg
Prednisolone	Different from patient to patient				

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. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Patient populations a) and b)

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					
Benralizumab 30 mg	1 PEN	€ 2,606.27	€ 1.77	€ 145.55	€ 2,458.95
Prednisolone 5 mg[9]	100 TAB	€ 15.43	€ 1.77	€ 0.33	€ 13.33
Prednisolone 20 mg[9]	100 TAB	€ 21.62	€ 1.77	€ 0.81	€ 19.04

[9] Fixed reimbursement rate

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
Appropriate comparator therapy					
Cyclophosphamide 200 mg	10 PSI	€ 69.60	€ 1.77	€ 3.23	€ 64.60
Cyclophosphamide 1,000 mg	6 PSI	€ 142.80	€ 1.77	€ 7.28	€ 133.75
Cyclophosphamide 1,000 mg	1 PSI	€ 33.24	€ 1.77	€ 1.21	€ 30.26
Mepolizumab 100 mg	3 SFI	€ 3,731.92	€ 1.77	€ 0.00	€ 3,730.15
Prednisolone 5 mg[9]	100 TAB	€ 15.43	€ 1.77	€ 0.33	€ 13.33
Prednisolone 20 mg[9]	100 TAB	€ 21.62	€ 1.77	€ 0.81	€ 19.04
Rituximab 500 mg	1 CIS	€ 782.56	€ 1.77	€ 36.60	€ 744.19
Abbreviations: FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; PEN = solution for injection in a pre-filled pen; PSI = powder for solution for injection TAB = tablets					

LAUER-TAXE® last revised: 15 April 2025

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.

Because there are no 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, no costs for additionally required SHI services need to be taken into account.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1 October 2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of

€ 100 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

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

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

Basic principles of the assessed medicinal product

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

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

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

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

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

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

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

Concomitant active ingredient

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

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

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

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

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

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

Medicinal products with new active ingredients for which the G-BA has decided on an

exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

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

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

Exception to the designation

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

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

Legal effects of the designation

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

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

Justification for the findings on designation in the present resolution:

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

The designated medicinal products concern in each case an active ingredient which may be used in combination therapy with the assessed medicinal product in the context of a therapeutic indication specified in the product information for the assessed medicinal product. According to the requirements in the product information, this therapeutic indication is an add-on treatment for adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis.

For the designated medicinal products, the prerequisites of Section 35a, paragraph 3, sentence 4 SGB V are fulfilled and, according to the requirements in the product information, there are no reasons for exclusion that prevent a combination therapy with the assessed medicinal product.

References:

Product information for benralizumab (Fasenra); solution for injection in a pre-filled syringe / Fasenra® 30 mg solution for injection in a pre-filled pen; last revised: October 2024

Product information for mepolizumab (Nucala); Nucala 100 mg solution for injection in a pre-filled pen / in a pre-filled syringe Nucala 40 mg solution for injection in a pre-filled syringe; last revised June 2024

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

The designated medicinal products concern in each case an active ingredient which may be used in combination therapy with the assessed medicinal product in the context of a therapeutic indication specified in the product information for the assessed medicinal product. According to the requirements in the product information, this therapeutic indication is an add-on treatment for adults with relapsing or refractory eosinophilic granulomatosis with polyangiitis.

For the designated medicinal products, the prerequisites of Section 35a, paragraph 3, sentence 4 SGB V are fulfilled and, according to the requirements in the product information, there are no reasons for exclusion that prevent a combination therapy with the assessed medicinal product.

References:

Product information for benralizumab (Fasenra); solution for injection in a pre-filled syringe / Fasenra® 30 mg solution for injection in a pre-filled pen; last revised: October 2024

Product information for mepolizumab (Nucala); Nucala 100 mg solution for injection in a pre-filled pen / in a pre-filled syringe Nucala 40 mg solution for injection in a pre-filled syringe; last revised June 2024

Supplement to Annex XIIa of the Pharmaceuticals Directive

Since the resolution under I.5 mentions medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V, which can be used in a combination therapy with the assessed active ingredient in the therapeutic indication of the resolution, the information on this designation is to be added to Annex XIIa of the Pharmaceuticals Directive and provided with patient-group-related information on the period of validity of the designation.

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 their session on 26 June 2018, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at their session on 23 January 2024.

On 21 November 2024, the pharmaceutical company submitted a dossier for the benefit assessment of benralizumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 25 November 2024 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 benralizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 February 2025, and the written statement procedure was initiated with publication on the G-BA website on 3 March 2025. The deadline for submitting statements was 24 March 2025.

The oral hearing was held on 7 April 2025.

By letter dated 8 April 2025, the IQWiG was commissioned with supplementary assessments. The addenda prepared by the IQWiG were submitted to the G-BA on 23 April and 25 April 2025.

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 6 May 2025, and the proposed draft resolution was approved.

At their session on 15 May 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	26 June 2018	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	23 January 2024	New determination of the appropriate comparator therapy
Working group Section 35a	2 April 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	7 April 2025	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	16 April 2025 30 April 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	6 May 2025	Concluding discussion of the draft resolution
Plenum	15 May 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 15 May 2025

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

Prof. Hecken