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Mepolizumab (eosinophilic granulomatosis with polyangiitis) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Mepolizumab (eosinophile Granulomatose mit Polyangiitis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 25 February 2022). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondent for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
ACT	appropriate comparator therapy
BVAS	Birmingham Vasculitis Activity Score
EGPA	eosinophilic granulomatosis with polyangiitis
EULAR	European League Against Rheumatism
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
OCS	oral corticosteroid
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug mepolizumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 30 November 2021.

Research question

The aim of the present report is to assess the added benefit of mepolizumab as an add-on treatment in comparison with the appropriate comparator therapy (ACT) for patients aged 6 years and older with relapsing-remitting or refractory eosinophilic granulomatosis with polyangiitis (EGPA).

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of mepolizumab

Therapeutic indication	**ACT[a]**
Add-on treatment for patients aged 6 years and older with relapsing-remitting or refractory EGPA	Individualized therapy, taking into account the severity of disease (organ- or life-threatening manifestation), symptoms, treatment phase, and course of disease[b,c]

a. Presented is the ACT specified by the G-BA.
b. Typically, EGPA treatment involves an induction phase and a maintenance phase. For patients with EGPA, guidelines recommend treatment with corticosteroids, combined where necessary with an immunosuppressant, depending on organ- or life-threatening manifestation, treatment phase, and course of disease. For individualized therapy within the framework of a clinical trial, suitable comparators are corticosteroids, if necessary in combination with the immunosuppressants of cyclophosphamide, rituximab, leflunomide, mycophenolate mofetil, methotrexate, and azathioprine. These immunosuppressants are not approved for EGPA treatment. This results in a discrepancy between the drugs approved for the indication versus those used in practice and recommended by the guidelines. Plasmapheresis is not deemed a regular part of individualized therapy.
c. Both study arms should allow modifying treatment based on the patient's individual needs. In this context, treatment modification can comprise both dose modifications and treatment switches/initiations to respond to newly arisen symptoms or the deterioration of existing symptoms.

ACT: appropriate comparator therapy; EGPA: eosinophilic granulomatosis with polyangiitis; G-BA: Federal Joint Committee

The company generally followed the G-BA's specification of the ACT. The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of added benefit.

Results

The check for completeness of the study pool revealed no relevant study for comparing mepolizumab versus the ACT. The company, in contrast, identified the RCT MIRRA and used it in its assessment. However, the MIRRA study is unsuitable for the benefit assessment of mepolizumab versus the ACT. This is explained below.

Evidence presented by the company – MIRRA RCT

The MIRRA RCT is a randomized, double-blind study comparing mepolizumab with placebo, each as an add-on to an oral corticosteroid (OCS) and if necessary an immunosuppressant in adult patients with EGPA. A total of 136 patients were randomly allocated in a 1:1 ratio to 52 weeks of treatment with either mepolizumab (N = 68) or placebo (N = 68), each as an add-on to OCS and an immunosuppressant if necessary. The study's patient population is heterogeneous since it included both patients with active disease and those with a history of recurrent or refractory disease. A total of 71% of patients in the control arm had active EGPA (Birmingham Vasculitis Activity Score [BVAS] ≥ 1) at baseline. The study excluded patients with organ-threatening EGPA within 3 months prior to screening as well as patients with life-threatening EGPA. The 2 primary outcomes were duration of remission and the percentage of patients in remission. In the MIRRA study, the latter was defined as BVAS = 0 and OCS dose ≤ 4 mg/day.

Appropriate comparator therapy not implemented

The MIRRA study is unsuitable for drawing conclusions on the added benefit of mepolizumab because it did not implement the ACT specified by the G-BA. For the implementation of individualized therapy, treatment modification is assumed to potentially comprise both dose modifications and treatment switches/initiations to respond to newly arisen symptoms or deterioration of existing symptoms. All patients included in the MIRRA study were to have been on a stable dose of OCS and possibly an immunosuppressant for at least 4 weeks prior to randomization. In the course of the study, treatment modification to meet the patients' individual needs without permanent discontinuation of the study medication was allowed only for OCS. OCS dose increases were allowed in the first 4 weeks as well as in case of relapse (a dose increase by more than 4mg/day was rated as a relapse). In patients who received an additional immunosuppressant at baseline, only 1 dose reduction for safety reasons was allowed, with a return to the original dose being implemented where possible. Patients with dose escalation or initiation of immunosuppressant therapy, in contrast, were excluded from further study treatment.

In the control arm, 82% of patients suffered ≥ 1 relapse over the course of the study, and about 81% of patients did not achieve remission as defined by the primary outcome at any point in the study. As per the European League Against Rheumatism (EULAR) definition of remission, about half (53%) of patients did not achieve remission at any point in the study, despite OCS dose modifications. These high percentages of control arm patients as well as the results of the subgroup analyses (characteristic of concomitant immunosuppressant treatment [yes/no]),

which show that the advantage of mepolizumab for the outcome of remission is more pronounced in patients without concomitant immunosuppressant therapy, suggest that further optimization by modification or initiation of immunosuppressant therapies might have been possible. Hence, it is unclear whether modification or initiation of immunosuppressant therapy in the control arm either at study start or in the further course would have prevented relapse or led to remission in some patients. Furthermore, the MIRRA study allowing treatment modification only for OCS represents an inadequate implementation of the ACT specified by the G-BA, even when considering the G-BA's note on treatment modification (see above). In an overall consideration of these aspects, the study submitted by the company therefore does not allow a comparison of mepolizumab versus the ACT specified by the G-BA.

Results on added benefit

For the assessment of mepolizumab as an add-on treatment for patients aged 6 years and older with relapsing-remitting or refractory EGPA, no suitable data are available to assess added benefit in comparison with the ACT. This results in no hint of added benefit of mepolizumab in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of the probability and extent of added benefit of mepolizumab.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Mepolizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Add-on treatment for patients aged 6 years and older with relapsing-remitting or refractory EGPA	Individualized therapy, taking into account the severity of disease (organ- or life-threatening manifestation), symptoms, treatment phase, and course of disease[b,c]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. Typically, EGPA treatment involves an induction phase and a maintenance phase. For patients with EGPA, guidelines recommend treatment with corticosteroids, combined where necessary with an immunosuppressant, depending on organ- or life-threatening manifestation, treatment phase, and course of disease. For individualized therapy within the framework of a clinical trial, suitable comparators are corticosteroids, if necessary in combination with the immunosuppressants of cyclophosphamide, rituximab, leflunomide, mycophenolate mofetil, methotrexate, and azathioprine. These immunosuppressants are not approved for EGPA treatment. This results in a discrepancy between the drugs approved for the indication versus those used in practice and recommended by the guidelines. Plasmapheresis is not deemed a regular part of individualized therapy.
c. Both study arms should allow modifying treatment based on the patient's individual needs. In this context, treatment adjustment can comprise both dose adjustments and treatment switches/initiations to respond to newly developed symptoms or the deterioration of existing symptoms.

ACT: appropriate comparator therapy; EGPA: eosinophilic granulomatosis with polyangiitis; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is to assess the added benefit of mepolizumab as an add-on treatment in comparison with the ACT for patients aged 6 years and older with relapsing-remitting or refractory EGPA.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of mepolizumab

Therapeutic indication	**ACT[a]**
Add-on treatment for patients aged 6 years and older with relapsing-remitting or refractory EGPA	Individualized therapy, taking into account the severity of disease (organ- or life-threatening manifestation), symptoms, treatment phase, and course of disease[b,c]

a. Presented is the ACT specified by the G-BA.
b. Typically, EGPA treatment involves an induction phase and a maintenance phase. For patients with EGPA, guidelines recommend treatment with corticosteroids, combined where necessary with an immunosuppressant, depending on organ- or life-threatening manifestation, treatment phase, and course of disease. For individualized therapy as part of a clinical trial, suitable comparators are corticosteroids, if necessary in combination with the immunosuppressants of cyclophosphamide, rituximab, leflunomide, mycophenolate mofetil, methotrexate, and azathioprine. These immunosuppressants are not approved for EGPA treatment. This results in a discrepancy between the drugs approved for the indication versus those used in practice and recommended by the guidelines. Plasmapheresis is not deemed a regular part of individualized therapy.
c. Both study arms should allow treatment adjustments based on the patient's individual needs. In this context, treatment adjustment can comprise both dose adjustments and treatment switches/initiations to respond to newly developed symptoms or the deterioration of existing symptoms.

ACT: appropriate comparator therapy; EGPA: eosinophilic granulomatosis with polyangiitis; G-BA: Federal Joint Committee

The company generally followed the G-BA's specification of the ACT. However, the company argues that cyclophosphamide and rituximab are not indicated for the mepolizumab target population because both drugs are indicated only for life-threatening EGPA and the MIRRA study used by the company (see Section 2.3) excluded patients with life-threatening manifestation. This view is not shared since the therapeutic indication of mepolizumab also comprises life-threatening manifestations [3,4].

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study lists on mepolizumab (status: 1 October 2021)
- bibliographical literature search on mepolizumab (last search on 4 October 2021)

- search in trial registries / trial results databases for studies on mepolizumab (last search on 4 October 2021)
- search on the G-BA website for mepolizumab (last search on 4 October 2021)

To check the completeness of the study pool:

- search in trial registries for studies on mepolizumab (last search on 13 December 2021); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any relevant studies for assessing the added benefit of mepolizumab in comparison with the ACT.

The data presented by the company are unsuitable for deriving an added benefit of mepolizumab in comparison with the ACT. This is justified below. For this purpose, the MIRRA study [5-9] included by the company is described first. Then, an explanation is provided as to why the data presented permit no derivation of conclusions on the added benefit.

Evidence provided by the company

The study pool of the company consists of the MIRRA RCT. This study included only adult patients. The company did not present any evidence on children aged 6 years and older who are also covered by the therapeutic indication. However, the company extrapolated the MIRRA study results from adults to children and adolescents aged 6 years and older. The company's Module 4 B justifies this approach by the extrapolation approach accepted by the European Medicines Agency (EMA). Since the MIRRA study is irrelevant for this benefit assessment, the company's approach for extrapolating the results is not commented further.

Study characteristics

The MIRRA study is a randomized double-blind study comparing mepolizumab with placebo, each as an add-on to an OCS and if necessary an immunosuppressant in adult patients with EGPA. The diagnosis had to have been established at least 6 months prior to screening.

No consensus exists on the diagnostic criteria for EGPA. The literature lists the Lanham criteria [10], the Chapel Hill Consensus Conference (CHCC) nomenclature [11] as well as the American College of Rheumatology (ACR) criteria [12] for a definition of EGPA. The MIRRA study used modified ACR criteria, and the EGPA diagnosis was based on patient history or the presence of asthma and eosinophilia as well as at least 2 further EGPA characteristics (see Table 9), which are, however, not all of the same diagnostic value.

The study comprises a heterogeneous patient population because both patients with active disease and patients with a history of recurrent or refractory disease were eligible for inclusion (for the definition of recurrent and refractory, see Table 9 in Appendix B of the full dossier assessment). However, a total of 71% of control arm patients had active EGPA (BVAS ≥ 1) at baseline.

Children and adolescents as well as patients with organ-threatening EGPA (organ failure due to active vasculitis, creatinine > 5.8 g/dL) within 3 months prior to screening or with life-threatening EGPA are included in the therapeutic indication but were excluded from study participation.

Overall, 136 patients were randomly allocated at a 1:1 ratio to 52 weeks of treatment with either mepolizumab (N = 68) or placebo (N = 68), each as an add-on to OCS and if necessary an immunosuppressant. Patients were stratified into 3 subgroups: participants of a mechanistic biomarker substudy in the United States, those recruited in Japan, and the remaining recruited patients.

In the MIRRA study, mepolizumab was administered in accordance with the SPC [3,4]. To maintain blinding, patients in the comparator arm received placebo. The add-on treatment consisting of OCS at a dose of ≥ 7.5mg/day and, if necessary, an immunosuppressant was to have remained constant for at least 4 weeks prior to randomization. OCS was taken daily or every 2 days, and the daily dose was recorded in an electronic diary. OCS dose adjustments were permitted (see Table 10 in Appendix B of the full dossier assessment). The use of immunosuppressants (e.g. leflunomide, mycophenolate mofetil, azathioprine), in contrast, was allowed only if the dose was kept stable from ≥ 4 weeks prior to study start until the end of the study. Cyclophosphamide and rituximab treatment was disallowed. At study start, 41 of 68 patients (60%) in the intervention arm and 31 of 68 patients (46%) in the control arm received an immunosuppressant.

The 2 primary outcomes were duration of remission and the percentage of patients in remission. In the MIRRA study, the latter was defined as BVAS = 0 and an OCS dose of ≤ 4 mg/day. Further patient-relevant outcomes were recorded in the categories of morbidity, health-related quality of life, and side effects.

Further information on the MIRRA study characteristics, the interventions used, and the included patients are found in Appendix B of the full dossier assessment.

Appropriate comparator therapy not implemented

For patients aged 6 years and older with relapsing-remitting or refractory EGPA, the G-BA designated as the ACT individualized therapy taking into account severity of disease (organ- or life-threatening manifestation), symptoms, treatment phase, and course of disease. In its comments on the ACT, the G-BA mentions that, for individualized therapy, glucocorticoids, if applicable in combination with the immunosuppressants cyclophosphamide, rituximab, leflunomide, mycophenolate, mofetil, methotrexate, and azathioprine, are listed in guidelines and deemed suitable comparators in the context of clinical trials, although these immunosuppressants are not approved for the treatment of EGPA. For the implementation of individualized therapy, treatment adjustment is assumed to potentially comprise both dose adjustments and treatment switches/initiations to respond to newly developed symptoms or deterioration of existing symptoms.

The MIRRA study's inclusion criteria allowed the participation of patients in remission (BVAS = 0 and OCS doge ≤ 7.5 mg/day as per EULAR recommendations for the conduct of clinical trials in systemic vasculitis [13]) as well as symptomatic (recurrent or refractory) patients. This makes it a heterogeneous study population which technically might be eligible at baseline for individualized OCS monotherapy or OCS-immunosuppressant combination therapy. The study excluded patients with organ- or life-threatening EGPA for whom a combination treatment consisting of OCS and cyclophosphamide or rituximab is indicated [14,15].

At randomization, all MIRRA study participants were to have been on a stable dose of OCS therapy for at least 4 weeks. The same applied to immunosuppressants in patients who received an additional immunosuppressant at the time of randomization (see above). Hence, investigators in the MIRRA study did not have a choice of several treatment options at baseline which would have allowed such individualized treatment optimization for patients who would have required a modification at that time. Furthermore, in the course of the study, treatment modification to meet the respective needs of patients without permanent discontinuation of the study medication was allowed only for OCS. Up to Week 4 after the start of treatment with the study medication, OCS dose increases were allowed if needed; after that, the OCS dose was to be reduced, where possible, in the presence of lower disease activity. A dose increase for relapse treatment was allowed, however, with dose increases beyond 4 mg/day being rated as relapse. In patients who received an additional immunosuppressant at baseline, only 1 dose reduction for safety reasons was allowed, with a return to the original dose being implemented where possible. It is unclear how many patients received such a dose reduction in the course of the study. A total of 46% of patients in the control arm received an immunosuppressant at baseline (60% in the intervention arm). In case of a dose escalation or initiation of immunosuppressant therapy, patients were excluded from further study treatment. In 1 patient in the intervention arm and 2 patients in the control arm, immunosuppressant therapy was initiated or the dose increased over the course of the study, which led to study drop-out in each case.

At baseline, only 6 patients were in remission as per EULAR definition (BVAS = 0 and OCS dose ≤ 7.5 mg/day), of which 2 were in the control arm (as per remission definition of the primary outcome [see above]; no one was in remission at baseline). The administered therapy can be safely assumed not to have required escalation only in these patients and in asymptomatic patients (BVAS = 0 and OCS dose > 7.5 mg/day), and this is the case only at baseline. However, a total of 71% of patients in the control arm had active EGPA (BVAS ≥ 1) at baseline. Assessing whether continuation or adjustment of the existing therapy was indicated for the individual patients at baseline requires additional knowledge about the therapy phase (induction, maintenance) and disease phase (recurrent or refractory) [14,15]. However, this information is not available. Due to the heterogeneous patient population (recurrent or refractory EGPA) in combination with missing information on treatment phase (induction or maintenance phase), it is impossible to estimate the number of patients for whom optimization of immunosuppressant therapy would have been indicated at baseline.

In the control arm, 82% of patients suffered ≥ 1 relapse over the course of the study, and 81% of patients did not achieve remission as defined by the primary outcome at any point in the study; as per EULAR definition of remission, about half (53%) of patients did not achieve remission at any point in the study, despite OCS dose adjustments. Due to these high percentages of patients in each case, it is safe to assume that modification or initiation of immunosuppressant therapy would have been indicated in several control arm patients. The subgroup analyses submitted by the company (attribute of immunosuppressant concomitant therapy [yes/no]) likewise suggest that immunosuppressant therapy might have prevented relapse or led to remission. According to these subgroup analyses, the advantage of mepolizumab regarding the outcome of remission is more pronounced in patients without immunosuppressant concomitant therapy than in patients who received it.

Irrespective of the above aspects, the sole OCS adjustment option available in the MIRRA study fundamentally departs from the ACT specified by the G-BA, even when taking into account the G-BA's note on treatment adjustment (see above). In addition, an add-on design using placebo as a comparator therapy is generally appropriate only where no further treatment escalation or optimization is possible in the control arm. However, particularly for patients with active EGPA, the present study suggests that further escalation or optimization of immunosuppressant therapy would have been indicated in the control arm.

Summary

Overall, the MIRRA study did not implement the ACT. By limiting modification options to OCS, the study precludes individualized therapy taking into account the severity of disease (organ- or life-threatening manifestation), symptoms, treatment phase, and course of disease. The low percentage of control arm patients who achieve remission as well as the high relapse rate suggest that immunosuppressant treatment escalation or optimization would have been possible and indicated in these patients.

For the above reasons, the presented data are unsuitable for assessing the added benefit of mepolizumab in comparison with the ACT.

2.4 Results on added benefit

For the assessment of mepolizumab as an add-on treatment for patients aged 6 years and older with relapsing-remitting or refractory EGPA, no suitable data are available to assess added benefit in comparison with the ACT. This results in no hint of added benefit of mepolizumab in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit of mepolizumab in comparison with the ACT.

Table 5: Mepolizumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Add-on treatment for patients aged 6 years and older with relapsing-remitting or refractory EGPA	Individualized therapy, taking into account the severity of disease (organ- or life-threatening manifestation), symptoms, treatment phase, and course of disease[b,c]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. Typically, EGPA treatment involves an induction phase and a maintenance phase. For patients with EGPA, guidelines recommend treatment with corticosteroids, combined where necessary with an immunosuppressant, depending on organ- or life-threatening manifestation, treatment phase, and course of disease. For individualized therapy as part of a clinical trial, suitable comparators are corticosteroids, where necessary in combination with the immunosuppressants of cyclophosphamide, rituximab, leflunomide, mycophenolate mofetil, methotrexate, and azathioprine. These immunosuppressants are not approved for EGPA treatment. This results in a discrepancy between the drugs approved for the indication versus those used in practice and recommended by the guidelines. Plasmapheresis is not deemed a regular part of individualized therapy.
c. Both study arms should allow modifying treatment based on the patient's individual needs. In this context, treatment adjustment can comprise both dose adjustments and treatment switches/initiations to respond to newly developed symptoms or the deterioration of existing symptoms.

ACT: appropriate comparator therapy; EGPA: eosinophilic granulomatosis with polyangiitis; G-BA: Federal Joint Committee

The assessment described above deviates from that by the company, which derived an indication of major added benefit based on the results of the MIRRA study.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a21-151.html.