IQWiG Reports – Commission No. A21-152

# Mepolizumab (hypereosinophilic syndrome) –

## 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 (hypereosinophiles Syndrom) – 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**

No feedback was received in the framework of the present 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 |
|---|---|
| ACT | appropriate comparator therapy |
| FIP1L1-PDGFR α | FIP1-like1-Platelet-Derived Growth Factor Receptor α |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| HES | hypereosinophilic syndrome |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| RCT | randomized controlled trial |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SPC | Summary of Product Characteristics |

# 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 29 November 2021.

### Research question

The aim of the present report is to assess the added benefit of mepolizumab as add-on therapy in comparison with treatment upon the physician's discretion as the appropriate comparator therapy (ACT) in adult patients with inadequately controlled hypereosinophilic syndrome (HES) without an identifiable non-haematological secondary cause.

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 therapy in adult patients with inadequately controlled HES without an identifiable non-haematological secondary cause[b] | Therapy upon the physician's discretion[d] |

a. Presented is the ACT specified by the G-BA.
b. The clinical studies on mepolizumab did not investigate patients with FIP1L1-PDGFRα translocation. According to the G-BA, due to disease aetiology, patients with clonal hypereosinophilia are currently assumed not to be candidates for mepolizumab treatment. Therefore, this patient group was disregarded in the G-BA's specification of the ACT.
c. No approved drug therapies exist for treating HES without FIP1L1-PDGFRα translocation. Even the drugs listed in treatment recommendations are not approved for treatment. The following drugs may be suitable comparators within a study: corticosteroids and potentially other immunosuppressants (azathioprine, interferon-α, or ciclosporin), or myelosuppressive therapy (hydroxycarbamide), or a treatment attempt with imatinib.
d. Unchanged continuation of an inadequate therapy does not constitute implementation of therapy upon the physician's discretion if, at the time of enrolment, treatment adjustment options are still available to optimize treatment.

ACT: appropriate comparator therapy; FIP1L1-PDGFRα: FIP1-like1-Platelet-Derived Growth Factor Receptor α; G-BA: Federal Joint Committee; HES: hypereosinophilic syndrome

The company followed the specification of the G-BA by designating therapy upon the physician's discretion as 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 studies comparing mepolizumab versus the ACT of therapy upon the physician's discretion. The company, in contrast, identified the RCT 200622 and used it in its assessment. However, the 200622 study is unsuitable for the benefit assessment of mepolizumab versus the ACT. This is explained below.

***Evidence presented by the company – 200622 study***

The 200622 study is a randomized double-blind study comparing mepolizumab with placebo, each in addition to standard therapy for HES. The study included patients with severe HES who had a history of at least 2 flares within 12 months prior to study inclusion and a blood eosinophil count of > 1000 cells/µL within 4 weeks prior to randomization. A total of 108 patients were randomized in a 1:1 ratio and allocated to treatment with mepolizumab or placebo.

In the study, mepolizumab treatment was dosed in accordance with the specifications of the Summary of Product Characteristics (SPC). Alongside mepolizumab or placebo, patients were to continue their baseline HES therapy at a stable dose throughout the study. Adjustment of this standard therapy was allowed only as part of flare treatment in case of symptom deterioration. After flare resolution, investigators were expected to return patients' HES therapy to the baseline regimen where medically appropriate.

The primary outcome of the 200622 study was the percentage of patients who experienced an HES flare. Further patient-relevant outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

***Therapy upon the physician's discretion not implemented in 200622 study***

The 200622 study is unsuitable for assessing any added benefit of mepolizumab in comparison with the ACT specified by the G-BA. Based on the ACT specified by the G-BA, corticosteroids and, if necessary, other cytotoxic/immunosuppressive drugs represent suitable comparators within a study. Unchanged continuation of an inadequate therapy does not constitute an implementation of therapy upon the physician's discretion if, at the time of enrolment, treatment adjustment options are still available for optimizing treatment.

In the 200622 study, 70% of comparator arm patients used oral corticosteroids or cytotoxic/immunosuppressive therapies as standard therapy at baseline. However, on the basis of the information submitted by the company, it remains unclear whether the included patients continued an inadequate therapy or whether at the time of enrolment, it would have been possible to adjust treatment to achieve treatment optimization. The study protocol did not provide for optimization of standard therapy. Only temporary adjustments of standard therapy were provided for as part of flare treatment. However, it can be safely assumed that participants of the 200622 study who had severe HES and current flares suffered from inadequately controlled disease and that they would have potentially benefited from optimization of standard therapy.

In the comparator arm, 26% of patients received neither oral corticosteroids nor cytotoxic/immunosuppressive therapies at baseline and hence did not receive any of the suitable comparators in the context of therapy upon the physician's discretion in accordance with the ACT specified by the G-BA. On the basis of the information presented by the company, it remains unclear whether for these patients, it would have been possible to optimize standard therapy by using such therapies.

In summary, the company did not submit any information as to whether or to what extent the 200622 study involved optimization of standard therapy as required for the ACT of therapy upon the physician's discretion. Therefore, the study presented by the company is unsuitable for comparing mepolizumab with the ACT of therapy upon the physician's discretion.

**Results on added benefit**

No suitable data are available to assess added benefit in comparison with the ACT for mepolizumab as an add-on treatment for adult patients with inadequately controlled HES without an identifiable non-haematological secondary cause. 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 therapy in adult patients with inadequately controlled HES without an identifiable non-haematological secondary cause[b] | Therapy upon the physician's discretion[c,d] | Added benefit not proven |

a. Presented is the respective ACT specified by the G-BA.
b. The clinical studies on mepolizumab did not investigate patients with FIP1L1-PDGFRα translocation. According to the G-BA, due to disease aetiology, patients with clonal hypereosinophilia are currently assumed not to be candidates for mepolizumab treatment. Therefore, this patient group was disregarded in the G-BA's specification of the ACT.
c. No approved drug therapies exist for treating HES without FIP1L1-PDGFRα translocation. Even the drugs listed in treatment recommendations are not approved for treatment. The following drugs may be suitable comparators within a study: corticosteroids and, if applicable, other immunosuppressants (azathioprine, interferon-α, or ciclosporin), or myelosuppressive therapy (hydroxycarbamide), or a treatment attempt with imatinib.
d. Unchanged continuation of an inadequate therapy does not constitute implementation of therapy upon the physician's discretion if at the time of enrolment, treatment adjustment options were still available to optimize treatment.

ACT: appropriate comparator therapy; FIP1L1-PDGFRα: FIP1-like1-Platelet-Derived Growth Factor Receptor α; G-BA: Federal Joint Committee; HES: hypereosinophilic syndrome

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 add-on therapy in comparison with treatment upon the physician's discretion as the ACT in adult patients with inadequately controlled HES without an identifiable non-haematological secondary cause.

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 therapy in adult patients with inadequately controlled HES without an identifiable non-haematological secondary cause[b] | Therapy upon the physician's discretion[d] |

a. Presented is the ACT specified by the G-BA.
b. The clinical studies on mepolizumab did not investigate patients with FIP1L1-PDGFRα translocation. According to the G-BA, due to disease aetiology, patients with clonal hypereosinophilia are currently assumed not to be candidates for mepolizumab treatment. Therefore, this patient group was disregarded in the G-BA's specification of the ACT.
c. No approved drug therapies exist for treating HES without FIP1L1-PDGFRα translocation. Even the drugs listed in treatment recommendations are not approved for treatment. The following drugs may be suitable comparators within a study: corticosteroids and, if necessary, other immunosuppressants (azathioprine, interferon-α, or ciclosporin), or myelosuppressive therapy (hydroxycarbamide), or a treatment attempt with imatinib.
d. Unchanged continuation of an inadequate therapy does not constitute implementation of therapy upon the physician's discretion if at the time of enrolment, treatment adjustment options were still available to optimize treatment.

ACT: appropriate comparator therapy; FIP1L1-PDGFRα: FIP1-like1-Platelet-Derived Growth Factor Receptor α; G-BA: Federal Joint Committee; HES: hypereosinophilic syndrome

The company followed the G-BA's specification of the ACT by designating therapy upon the physician's discretion as 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. 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 for completeness of the study pool revealed no relevant studies comparing mepolizumab versus the ACT of therapy upon the physician's discretion.

The company, in contrast, identified the 200622 RCT [3-7] and used it for its assessment. The 200622 study is unsuitable for the benefit assessment of mepolizumab versus the ACT. This is explained below.

**Evidence provided by the company**

The 200622 RCT submitted by the company compares mepolizumab with placebo, each in addition to standard HES therapy. The study is unsuitable for the present benefit assessment because the information submitted by the company fails to demonstrate that the standard therapy administered in the study's comparator arm was an implementation of the G-BA's specified ACT of therapy upon the physician's discretion.

***Design of the 200622 study***

The 200622 study is a randomized double-blind study comparing mepolizumab with placebo, each in addition to standard therapy for HES. The study included patients with severe HES who had a history of at least 2 flares within 12 months prior to study inclusion and a blood eosinophil count of > 1000 cells/µL within 4 weeks prior to randomization. The study excluded patients with FIP1-like1-Platelet-Derived Growth Factor Receptor α (FIP1L1-PDGFRα) translocation as well as patients with life-threatening HES or life-threatening comorbidities of HES.

A total of 108 patients were randomly allocated in a 1:1 ratio to treatment with mepolizumab (N = 54) or placebo (N = 54). According to the inclusion criteria, patients had to be on a stable dose of HES therapy for 4 weeks prior to randomization and maintain this stable dose throughout the study's treatment phase. The baseline HES therapy was allowed to include oral corticosteroids as well as immunosuppressive and cytotoxic therapies, but it was not limited to these drug classes. The study excluded patients not responding to oral corticosteroids as well as patients with hypersensitivity to steroids. Randomization was stratified by the factor of geographic region.

From randomization throughout the 32-week treatment phase, patients received either mepolizumab or placebo in the form of subcutaneous injections every 4 weeks in addition to their existing baseline HES therapy. The mepolizumab dosage used in the study was in accordance with the specifications of the SPC [8,9]. Patients were to continue their baseline stable HES therapy as an add-on therapy. Adjustment of this standard therapy was allowed only as part of flare treatment in case of symptom deterioration. The study protocol provided for flare treatment under the following conditions:

- In case of deterioration of clinical symptoms, the investigator was allowed to temporarily adjust the existing HES therapy (dose escalation or addition of new drugs).
- In patients who had not had any treatment adjustment due to symptom deterioration within the prior 2 weeks, blinded administration of oral corticosteroids according to a pre-specified dosing scheme was provided for in case of doubling of the blood eosinophil count or an increase by 2500 cells/µL, each from baseline (for details, see Table 11 in Appendix B of the full dossier assessment).

In both situations, the underlying event was rated as an HES flare. After flare resolution, investigators were expected to return patients' HES therapy to the baseline regimen where medically appropriate. The 200622 study protocol did not provide for optimization of the existing HES therapy at baseline.

The primary outcome of the 200622 study was the percentage of patients who experienced an HES flare. Further patient-relevant outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

Appendix B of the full dossier assessment provides further information on the 200622 study characteristics, the interventions used, and the included patients as well as baseline HES therapy.

***Therapy upon the physician's discretion not implemented in 200622 study***

The 200622 study is unsuitable for assessing any added benefit of mepolizumab in comparison with the ACT specified by the G-BA. As per the ACT specified by the G-BA, the following comparators are suitable for use within a study as the implementation of therapy upon the physician's discretion: corticosteroids and, if necessary, other immunosuppressants (azathioprine, interferon-α, or ciclosporin), or myelosuppressive therapy (hydroxycarbamide), or a treatment attempt with imatinib. Unchanged continuation of an inadequate therapy does not constitute an implementation of therapy upon the physician's discretion if, at the time of enrolment, treatment adjustment options are still available for optimizing treatment. In the 200622 study, 70% of patients in the comparator arm used oral corticosteroids or cytotoxic/immunosuppressive therapies as standard therapy at baseline (see Table 13 in Appendix B of the full dossier assessment). However, on the basis of the information submitted by the company, it remains unclear whether the included patients continued an inadequate therapy or whether at the time of enrolment, it would have been possible to adjust treatment to achieve treatment optimization.

The study protocol did not provide for optimization of standard therapy. Patients in the study's comparator arm had to continue their baseline HES therapy at a stable dose throughout the study's treatment phase. The study allowed temporary adjustments of standard therapy as part of the treatment of disease flares, but after flare resolution, the investigator was expected to resume the baseline regimen of the standard therapy where medically appropriate (see Table 11 in Appendix B of the full dossier assessment). The company's dossier does not provide any

information as to whether or to what extent patients in the comparator arm received adjustments of standard therapy over the course of the study independently of flare treatment (e.g. dose escalation or addition of new drugs). Further, the company's dossier does not provide any information on the prior treatment received by the included patients. On the basis of the available information, it is therefore impossible to determine whether, at enrolment, the patients' available treatment options in the context of standard therapy had already been exhausted or whether treatment adjustments would have been available (e.g. in the form of adjustments of the oral corticosteroid dosage or treatment attempts with cytotoxic/immunosuppressive medications). However, it can be safely assumed that participants of the 200622 study who had severe HES and current flares suffered from inadequately controlled disease and that they would have potentially benefited from optimization of standard therapy.

Furthermore, 26% of patients in the 200622 study's comparator arm received, at baseline, neither oral corticosteroids nor a cytotoxic/immunosuppressive therapy and hence received none of the suitable comparators specified as ACTs by the G-BA (see Table 13 of Appendix B of the full dossier assessment). On the basis of the information presented by the company, it remains unclear whether therapy with the above drugs would have been suitable for this patient group. However, given that the 200622 study excluded both patients not responding to oral corticosteroids and patients with steroid hypersensitivity, optimization of standard therapy seems likely to have constituted an option for these patients.

In summary, the company did not submit any information on whether or to what extent the 200622 study involved optimization of standard therapy as required in the context of the ACT of therapy upon the physician's discretion. In addition, for a relevant percentage of comparator arm patients, standard therapy at baseline included none of the suitable comparators available for therapy upon the physician's discretion as per the ACT specified by the G-BA. Therefore, the study presented by the company is unsuitable for comparing mepolizumab with the ACT of therapy upon the physician's discretion.

Irrespective of the 200622 study being unsuitable for the benefit assessment for the reasons discussed above, the following further uncertainties exist regarding the included patient population:

- As per the study protocol, the 200622 study included adolescents and adults. However, the therapeutic indication of mepolizumab is limited to adult patients. In fact, the study included only 4 adolescents and hence a low percentage (4%) of patients under 18 years of age (see Table 12 in Appendix B of the full dossier assessment).
- The research question of the present benefit assessment concerns patients without clonal hypereosinophilia. The 200622 study did exclude patients with FIP1L1-PDGFRα translocation. Since the study did not involve any investigations on other translocations, it remains unclear, however, whether the study included patients with other mutations causing clonal hypereosinophilia. Yet, with the FIP1L1-PDGFRα translocation, the study

excluded the most common cause of clonal hypereosinophilia. Therefore, this uncertainty is expected to remain of no consequence for the present benefit assessment.

## 2.4 Results on added benefit

No suitable data are available to assess added benefit in comparison with the ACT for mepolizumab as an add-on treatment for adult patients with inadequately controlled HES without an identifiable non-haematological secondary cause. 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 therapy in adult patients with inadequately controlled HES without an identifiable non-haematological secondary cause[b] | Therapy upon the physician's discretion[c,d] | Added benefit not proven |

a. Presented is the respective ACT specified by the G-BA.
b. The clinical studies on mepolizumab did not investigate patients with FIP1L1-PDGFRα translocation. According to the G-BA, due to disease aetiology, patients with clonal hypereosinophilia are currently assumed not to be candidates for mepolizumab treatment. Therefore, this patient group was disregarded in the G-BA's specification of the ACT.
c. No approved drug therapies exist for treating HES without FIP1L1-PDGFRα translocation. Even the drugs listed in treatment recommendations are not approved for treatment. The following drugs may be suitable comparators within a study: corticosteroids and, if necessary, other immunosuppressants (azathioprine, interferon-α, or ciclosporin), or myelosuppressive therapy (hydroxycarbamide), or a treatment attempt with imatinib.
d. Unchanged continuation of an inadequate therapy does not constitute implementation of therapy upon the physician's discretion if, at the time of enrolment, treatment adjustment options are still available to optimize treatment.

ACT: appropriate comparator therapy; FIP1L1-PDGFRα: FIP1-like1-Platelet-Derived Growth Factor Receptor α; G-BA: Federal Joint Committee; HES: hypereosinophilic syndrome

The assessment described above deviates from that by the company, which derived an indication of major added benefit based on the results of the 200622 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

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. GlaxoSmithKline. A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of mepolizumab in the treatment of adolescent and adult subjects with severe hypereosinophilic syndrome (HES-200622_!Study-Report-amend1). 2020.

4. GlaxoSmithKline. Synopsis for study 200622 (AMICE_2019). 2020.

5. GlaxoSmithKline. Study 200622: A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of mepolizumab in the treatment of adolescent and adult subjects with severe hypereosinophilic syndrome [online]. [Accessed: 17.12.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-001232-11.

6. GlaxoSmithKline. Efficacy and Safety Study of Mepolizumab in Subjects With Severe Hypereosinophilic Syndrome (HES) [online]. 2020 [Accessed: 17.12.2021]. URL: https://ClinicalTrials.gov/show/NCT02836496.

7. Roufosse F, Kahn J-E, Rothenberg ME et al. Efficacy and safety of mepolizumab in hypereosinophilic syndrome: A phase III, randomized, placebo-controlled trial. J Allergy Clin Immunol 2020; 146(6): 1397-1405.

8. GlaxoSmithKline. Nucala 100 mg Pulver zur Herstellung einer Injektionslösung [online]. 2021 [Accessed: 20.12.2021]. URL: http://www.fachinfo.de.

9. GlaxoSmithKline. Nucala 100 mg Injektionslösung im Fertigpen, Nucala 100 mg Injektionslösung in einer Fertigspritze [online]. 2021 [Accessed: 22.12.2021]. URL: http://www.fachinfo.de.

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