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 Mepolizumab (new therapeutic indication: hypereosinophilic syndrome (HES))

of 19 May 2022

Contents

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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 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 mepolizumab (Nucala) was listed for the first time on 1 February 2016 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 12 November 2021, GlaxoSmithKline GmbH & Co. KG 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 amendments to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 24 November 2021, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction

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with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient Chapter 8 (1) number 2 of the G-BA's Rules of Procedure (VerfO) on the active ingredient mepolizumab with the new therapeutic indication hypereosinophilic syndrome.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 March 2022, 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 mepolizumab 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, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by IQWiG. 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 mepolizumab.

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 Mepolizumab (Nucala) in accordance with the product information

Nucala is indicated as an add-on treatment for adult patients with inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause.

Therapeutic indication of the resolution (resolution of 19 May 2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause

Appropriate comparator therapy for mepolizumab:

Therapy according to doctor's instructions

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

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.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. The active ingredient imatinib is approved for the treatment of adults with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement.

on 2. For the treatment of a hypereosinophilic syndrome, no non-medicinal treatments are considered as appropriate comparator therapy.

on 3. In the mentioned therapeutic indication, there are no resolutions approved by the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V or non-medicinal treatments.

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 indication and is presented in the “Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V”.

In summary, it should be noted that the robust evidence on medicinal treatment options in the present therapeutic indication is limited.
No relevant Cochrane reviews or systematic reviews could be identified. The recommendations of a British guideline for the investigation and management of eosinophilia were included in the evidence synopsis, based on a systematic search and assessment of the evidence up to 2015. In the absence of current higher-quality evidence, the National Comprehensive Cancer Network (NCCN) guideline on the treatment of myeloid/lymphoid neoplasia (myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase fusion genes) was added to the evidence synopsis.
According to the guidelines, treatment of idiophatic hypereosinophilic syndrome (HES) with corticosteroids is primarily recommended; in addition, therapy with other

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immunosuppressants (e.g. azathioprine, interferon α, cyclosporin A) or myelosuppressive therapy (hydroxycarbamide) or a therapy trial with imatinib may be considered. In clinical practice, taking into account the heterogeneity of the disease and the different organ manifestations, topical and inhaled corticosteroids are also used as possible anti-inflammatory treatment options in addition to oral corticosteroids. According to the guidelines, patients with the lymphocytic variant of hypereosinophilic syndrome (HES) should be treated in the same way as patients with idiopathic HES. For patients with clonal eosinophilia with FIP1L1-PDGFRα rearrangement, the guidelines recommend therapy with the tyrosine kinase inhibitor imatinib. For patients with other genetic aberrations, various tyrosine kinase inhibitors are recommended in the chronic phase. However, these patients with FIP1L1-PDGFRα rearrangement were not studied in the clinical studies on mepolizumab. The G-BA assumes – also taking into account the statements of the clinical experts – that patients with clonal hypereosinophilia are not eligible for treatment with mepolizumab due to the aetiology of the disease. Therefore, this patient group is not considered when determining the appropriate comparator therapy.

No medicinal treatments are approved for the treatment of hypereosinophilic syndrome without FIP1L1-PDGFRα rearrangement. The active ingredients mentioned in the therapy recommendations are also not approved for the treatment. The following active ingredients may be suitable as comparators in a study: corticosteroids and possibly other immunosuppressants (azathioprine, interferon α or ciclosporin) or myelosuppressive therapy (hydroxycarbamide) or a therapy trial with imatinib. It is expected that the study doctor will be able to choose from several treatment options (multi-comparator study). The selection and, if necessary, limitation of treatment options must be justified. Any therapy adjustment indicated for the patient as part of the therapy according to the doctor's instructions should be made.
However, the possibility of the off-label use of the active ingredients in a clinical study does not allow any conclusions to be drawn about their appropriateness in the off-label use in the standard care of insured persons in the SHI system. Such an assessment would be reserved for the decision according to Section 35c SGB V. This does not affect an off-label prescription in specific cases according to the criteria of the established case law of the Federal Social Court on off-label use not regulated in the Pharmaceuticals Directive.

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

2.1.3 Extent and probability of the additional benefit

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

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There is hint for a considerable additional benefit for mepolizumab as an add-on treatment in adult patients with inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause.

Justification:

The pharmaceutical company submits the 200622 study for the assessment of the additional benefit of mepolizumab in adults with inadequately controlled hypereosinophilic syndrome (HES) without an identifiable non-haematologic secondary cause. The 200622 study was a randomised, double-blind study comparing mepolizumab with placebo, each in addition to a standard therapy for HES. The study was divided into a screening phase of up to four weeks, a treatment phase of 32 weeks and a follow-up of up to eight weeks. A total of 108 adolescents (≥ 12 years) and adults with severe HES who had at least two disease relapses within 12 months prior to the time of enrolment in the study and a blood eosinophil count of > 1000 cells/µl within four weeks prior to randomisation were enrolled in the study. Patients with FIP1L1-PDGFRα rearrangement and patients with life-threatening HES or life-threatening comorbidities of HES were excluded from the study. The enrolled patients should have received a stable medication of their HES therapy within four weeks prior to randomisation and should maintain it stable during the treatment phase of the study. HES therapy could include oral corticosteroids and immunosuppressive and cytotoxic therapies, but was not limited to these product classes. Adjustment of this standard therapy was possible in case of deterioration of symptoms as part of the treatment of disease relapses. After the episode has subsided, the dosage should be reduced again - if medically appropriate.

The primary endpoint of the 200622 study was the percentage of patients with HES disease relapse (HES relapse).

The study was conducted between March 2017 and August 2019 in Argentina, Belgium, Brazil, France, Germany, Italy, Mexico, Poland, Romania, Russia, Spain, the United Kingdom and the United States.

The comparator therapy in the sense of an unchanged continuation of the HES therapy existing at baseline until the occurrence of a relapse appears acceptable in this case, as the patients had been receiving a stable therapy for at least four weeks before randomisation and were in a clinically stable condition. In addition, a long-term increase in immunosuppressive therapy outside of a relapse is not indicated due to the side effect profile. However, uncertainties exist in the implementation of the comparator therapy, as 26% of patients in the comparator arm received neither oral corticosteroids nor cytotoxic/ immunosuppressive therapies at start of study. The documents submitted did not reveal for how many patients systemic therapy could be dispensed with due to specific organ involvement, which other HES therapies these patients received and whether and to what extent these contained topical or local corticosteroids, which also represent treatment options in clinical practice.

Eight per cent of the enrolled patients did not receive any HES-specific therapy at baseline. It remains unclear why this percentage of patients (7% in the mepolizumab arm and 9% in the control arm) were not eligible for any type of medicinal basic therapy. Notably, this meant that 9% of patients in the control arm did not receive HES-specific therapy outside of a relapse.

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Taken together, the implementation of the appropriate comparator therapy is considered to be a sufficient approximation to the appropriate comparator therapy despite the addressed uncertainties due to the heterogeneous clinical picture and the correspondingly heterogeneous treatment options as well as the inclusion criteria of the study.

No appropriate subgroup analyses were submitted as part of the benefit assessment.

Extent and probability of the additional benefit

Mortality

In the 200622 study, one death occurred in the mepolizumab arm by week 32. The result is not statistically significant.

Morbidity

Clinically manifested HES relapses

For the present benefit assessment, evaluations of the percentage of patients with ≥ 1 clinically manifested HES relapse are used, as these events are associated with symptomatology that are noticeable for the patients. In addition, the pharmaceutical company submitted further evaluations on HES relapses, which include HES relapses defined over two or more cycles of OCS treatment. The study protocol provided for OCS treatment according to a predefined dosing scheme, regardless of symptoms, if the blood eosinophil count had doubled or increased by 2500 cells/µl. Due to the unclear patient relevance of laboratory parameters, only clinically-manifested HES relapses are considered for the benefit assessment.

There was a statistically significant advantage for mepolizumab over placebo, in each case in combination with a standard therapy.

Fatigue: Brief Fatigue Inventory (BFI)

Fatigue was assessed in the 200622 study by BFI item 3 (fatigue of highest intensity) and by BFI total score (intensity of fatigue / impairment due to fatigue).

For the endpoint of fatigue, no statistically significant differences between the treatment arms were detected at week 32.

Severity of the HES symptoms (HES-DS)

In the 200622 study, symptomatology severity for different organ systems was assessed via an electronic diary (HES-DS). For the benefit assessment, both continuous evaluations for individual symptoms and responder analyses for the most distressing symptoms were presented. The latter were not taken into account for the benefit assessment, as this required the pre-selection of up to three most distressing symptoms at the start of the study, and this condition meant that not all study participants were included in the evaluation.

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Muscle/ joint pain; nasal or sinus symptoms; skin symptoms

No statistically significant difference was detected between the treatment arms based on the mean differences.

Chills or sweats; abdominal pain or flatulence; respiratory symptoms

The evaluations based on mean differences showed a statistically significant difference in each case to the advantage of mepolizumab + standard therapy compared to placebo + standard therapy. However, the 95% confidence interval of the standardised mean difference is not completely outside the irrelevance range of -0.2 to 0.2 in each case. Thus, it cannot be inferred that the effect is clinically relevant.

Activity impairment (WPAI)

The Work Productivity and Activity Impairment (WPAI) surveyed in the 200622 study is an instrument for recording primarily health economic aspects related to the impairment of work productivity and activities within the last 7 days. The questionnaire includes 6 questions covering overall work productivity and limitation of daily activities, and can be adapted to a specific disease.

Scores are calculated based on the questions, indicating the percentage of impairment due to the disease: Absence from work due to impairment by the disease (absenteeism), impairment by the disease at work (presenteeism), impairment of work by the disease (absenteeism + presenteeism) and impairment of daily activities by the disease. The evaluations of absenteeism, presenteeism and impairment of work due to the disease only include values from patients who were in employment at the start of the study.

For the benefit assessment, the evaluations for absenteeism and presenteeism of the WPAI are not taken into account. However, the impairment of daily activities due to the disease (question 6) addresses a patient-relevant aspect.

For this endpoint, operationalised as mean change at week 32, there was a statistically significant advantage in the mepolizumab arm over the placebo arm. The result is considered a relevant effect because the 95% confidence interval of the standardised mean difference is completely outside the irrelevance range of -0.2 to 0.2.

Patient-assessed treatment response (RTS) and patient-assessed symptom severity (SSR)

For the endpoints of patient-assessed treatment response (RTS) and patient-assessed symptom severity (SSR), no usable data are available for the benefit assessment.

PROMIS and modified MSAS-SF

The endpoint "physical functioning and sleep", which was collected in the 200622 study via the Patient Reported Outcome Measurement Information System (PROMIS), could not be used in the benefit assessment because the study-specific operationalisation was not

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sufficiently validated in the dossier. The same applies to the endpoint "burden of symptomatology", which was assessed using a modified form of the Memorial Symptom Assessment Scale-Short Form (MSAS-SF).

Quality of life

SF-36v2 – physical and mental component score

The Health Survey Short Form 36 (SF-36) is a generic instrument for measuring health-related quality of life, consisting of eight domains and a total of 36 questions. The physical sum scale (PCS) and the mental sum scale (MCS) of the generic quality-of-life questionnaire SF-36 were used in the assessment.

For the benefit assessment, the analyses on the improvement by 15% of the scale range at week 32 are used. For the physical component score (PCS) of the SF-36v2, based on the responder analysis for improvement by ≥ 9.4 points, there is a statistically significant difference to the advantage of mepolizumab + standard therapy compared to placebo + standard therapy. For the mental component score (MCS) of the SF-36v2, there is no statistically significant difference between the treatment groups based on the responder analysis for improvement by ≥ 9.6 points.

Side effects

SAEs, discontinuation due to AEs

There were no statistically significant differences between the treatment groups for the endpoints of SAEs and discontinuation due to AEs.

Overall assessment / conclusion

The benefit assessment is based on the randomised controlled trial 200622 in which mepolizumab was compared with placebo, in each case in addition to a standard therapy for the treatment of HES. Data are available on the endpoint categories of mortality, morbidity, quality of life and side effects. The results are based on the data cut-off at the end of the treatment phase in week 32.

In the endpoint category of mortality, there was no statistically significant difference in overall survival.

In the endpoint category of morbidity, the endpoints of clinically manifested HES relapses and activity impairment (WPAI question 6) showed a statistically significant advantage of mepolizumab over placebo. There were no statistically significant or clinically relevant differences between the treatment arms in the endpoints of fatigue and severity of HES symptoms.

In the endpoint category of health-related quality of life, the SF-36 showed a statistically significant advantage of mepolizumab for the physical component score, while the mental component score showed no statistically significant differences.

In the endpoint category of side effects, there is neither an advantage nor a disadvantage for treatment with mepolizumab + standard therapy compared to placebo + standard therapy.

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In the overall assessment, the positive effects of mepolizumab on the morbidity endpoints of clinically manifested HES relapses and activity impairment, as well as on health-related quality of life (physical component score of the SF-36) compared to the appropriate comparator therapy, are assessed as a previously unachieved significant improvement of the therapy-relevant benefit. The extent of the additional benefit is classified as considerable.

Thus, overall, a considerable additional benefit of mepolizumab as an add-on treatment over therapy according to doctor's instructions of adult patients with inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause can be derived.

Reliability of data (probability of additional benefit)

The assessment of the additional benefit is based on a randomised and direct comparator study. At the time of the data cut-off, all patients enrolled had been treated for 32 weeks. The cross-endpoint risk of bias is rated as low for the study.
However, uncertainties exist with regard to the implementation of the appropriate comparator therapy. At the start of the study, 26% of patients in the comparator arm were receiving neither oral corticosteroids nor cytotoxic/ immunosuppressive therapies. No information was provided on what other HES-specific therapies were offered, and whether HES therapy at the start of the study was appropriate to the underlying organ involvement.

Overall, therefore, a hint is derived for the reliability of data.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient mepolizumab. The therapeutic indication assessed here is as follows: "as an add-on treatment in adult patients with inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause".

The appropriate comparator therapy was determined by G-BA to be a “therapy according to doctor's instructions”.

The pharmaceutical company presents results based on the RCT 200622 in which mepolizumab was compared to placebo, in each case in addition to a standard therapy for the treatment of HES.

There is no statistically significant difference for the endpoint of overall survival.

In the endpoint category of morbidity, the endpoints of clinically manifested HES relapses and activity impairment (WPAI question 6) each show a statistically significant advantage of mepolizumab. There were no statistically significant or clinically relevant differences between the treatment arms in the endpoints of fatigue and severity of HES symptoms.

For health-related quality of life, there are advantages of mepolizumab over placebo in the physical component score and no differences in the mental component score.

There are no statistically significant differences in the area of side effects.

Uncertainties remain in the implementation of the appropriate comparator therapy, as 26% of patients in the comparator arm received neither oral corticosteroids nor cytotoxic/

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immunosuppressive therapies and no information is available on whether and to what extent non-systemic corticosteroids were used.

In the overall assessment, a hint for a considerable additional benefit is identified.

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 G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier, which are, however, subject to uncertainty. On the one hand, not all relevant patients may have been included in the pharmaceutical company's assumptions on prevalence, and on the other, the upper and lower limits determined for deriving the percentage of patients with HES in Germany based on literature data are fraught with uncertainty. In addition, the target population is not restricted to patients with inadequate disease control. The derived patient numbers also include an unclear percentage of patients with clonal hypereosinophilia. Overall, an underestimation or overestimation of the number of patients can be assumed.

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 Nucala (active ingredient: mepolizumab) at the following publicly accessible link (last access: 9 February 2022):

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

Treatment with mepolizumab should only be initiated and monitored by doctors experienced in treating hypereosinophilic syndrome.

Mepolizumab is intended for long-term treatment. The need for continued therapy should be reviewed at least once a year. Patients who develop life-threatening manifestations of HES should also be evaluated for the need for continued therapy as mepolizumab has not been studied in this patient group.

Patients who were FIP1L1-PDGFRα-kinase positive were excluded from the study.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 May 2022).

Mepolizumab is indicated as an add-on treatment in adult patients with inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause. Treatment of the occurring disease symptoms is also carried out with the administration of mepolizumab according to doctor's instructions. The type and scope of the therapy according to doctor's instructions can vary depending on the medicinal product to be assessed and the comparator therapy.

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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				
Mepolizumab	1 x every 28 days	13	1	13
Therapy according to doctor's instructions	No data available			
Appropriate comparator therapy				
Therapy according to doctor's instructions	No data available			
Corticosteroids and possibly other immunosuppressants (azathioprine, interferon α or ciclosporin) or myelosuppressive therapy (hydroxycarbamide) or a therapy trial with imatinib are considered suitable comparators for therapy according to doctor's instructions. These are not approved in the present therapeutic indication and therefore no costs are represented for these regimens.				

Consumption:

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 is patient-individual 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.

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					
Mepolizumab	300 mg	300 mg	3 x 100 mg	13	39 x 100 mg
Therapy according to doctor's instructions	No data available				

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Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Appropriate comparator therapy					
Therapy according to doctor's instructions	No data available				
Corticosteroids and possibly other immunosuppressants (azathioprine, interferon α or ciclosporin) or myelosuppressive therapy (hydroxycarbamide) or a therapy trial with imatinib are considered suitable comparators for therapy according to doctor's instructions. These are not approved in the present therapeutic indication and therefore no costs are represented for these regimens.					

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 Section 130 and Section 130a 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.

Costs of the medicinal products:

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					
Mepolizumab 100 mg	3 SFI	€ 3,731.89	€ 1.77	€ 0.00	€ 3,730.12
Therapy according to doctor's instructions	No data available				
Appropriate comparator therapy					
Therapy according to doctor's instructions	No data available				
Abbreviations: SFI = solution for injection					

LAUER-TAXE® last revised: 1 May 2022

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there

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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 had to be taken into account.

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 its session on 24 September 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. At its session on 23 November 2021, the Subcommittee on Medicinal Products made an adjustment to the notes on the defined appropriate comparator therapy.

On 24 November 2021, the pharmaceutical company submitted a dossier for the benefit assessment of mepolizumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 29 November 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits 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 mepolizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 25 February 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 1 March 2022. The deadline for submitting written statements was 22 March 2022.

The oral hearing was held on 11 April 2022.

By letter dated 12 April 2022, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by the IQWiG was submitted to the G-BA on 6 May 2022.

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.

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The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 10 May 2022, and the proposed resolution was approved.

At its session on 19 May 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	24 September 2019	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	23 November 2021	Implementation of the appropriate comparator therapy
Working group Section 35a	5 April 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	11 April 2022	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	20 April 2022 3 May 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	10 May 2022	Concluding discussion of the draft resolution
Plenum	19 May 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 19 May 2022

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

Prof. Hecken

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