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)
Tezepelumab (bronchial asthma, ≥ 12 years)

of 12 May 2023

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 relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient tezepelumab on 15 November 2022 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 14 November 2022.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 February 2023 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

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The G-BA came to a resolution on whether an additional benefit of tezepelumab compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. 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 tezepelumab.

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 Tezepelumab (Tezspire) in accordance with the product information

Tezspire is indicated as an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma who are inadequately controlled despite high dose inhaled corticosteroids plus another medicinal product for maintenance treatment.

Therapeutic indication of the resolution (resolution of 12 May 2023):

- see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adolescents 12 to 17 years with severe asthma who are inadequately controlled despite high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

Appropriate comparator therapy:

a patient-individual therapy escalation, taking into account the previous therapy with selection of:

- high-dose ICS and LABA and LAMA *or*
- high-dose ICS and LABA and, if necessary, LAMA and omalizumab, provided that the criteria necessary for the administration of omalizumab are met *or*

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

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- high-dose ICS and LABA and, if necessary, LAMA and mepolizumab or dupilumab, provided that the criteria necessary for the administration of omalizumab are met

b) Adults with severe asthma who are inadequately controlled despite high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

Appropriate comparator therapy:

a patient-individual therapy escalation taking into account the previous therapy and the pathogenesis of the asthma under selection of:

- high-dose ICS and LABA and LAMA *or*
- high-dose ICS and LABA and, if necessary, LAMA and omalizumab, provided that the criteria necessary for the administration of omalizumab are met *or*
- high-dose ICS and LABA and, if applicable, LAMA and mepolizumab or reslizumab or benralizumab or dupilumab, provided the criteria necessary for the use of the respective antibodies are met

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. Generally approved for the treatment of asthma are active ingredients of different product classes:

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- Selective beta-2-adrenergic receptor agonists: Salbutamol, fenoterol, reproterol, salmeterol, formoterol, terbutaline, salbutamol, bambuterol and clenbuterol
- Inhaled anticholinergics: Tiotropium bromide
- Inhaled corticosteroids: Beclometasone, budesonide, ciclesonide, fluticasone and mometasone
- Oral corticosteroids: e.g.: prednisolone or prednisone
- Combination preparations: Beclometasone/formoterol, budesonide/formoterol, formoterol/fluticasone, salmeterol/fluticasone, vilanterol/fluticasone, ipratropium/fenoterol, clenbuterol/ambroxol, indacaterol/glycopyrronium/mometasone and beclometasone/formoterol/glycopyrronium
- Other: Theophylline, omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab

on 2. For the treatment of not adequately controlled severe asthma, no non-medical measures can be considered as the sole appropriate comparator therapy.

on 3. The following resolutions on an amendment of the Pharmaceuticals Directive (AM-RL) are available:

Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V:

- Mepolizumab (resolution of 21 July 2016 and 22 March 2019)
- Reslizumab (resolution of 6 July 2017)
- Benralizumab (resolution of 2 August 2018)
- Dupilumab (resolution of 20 February 2020 and 6 October 2022)
- Indacaterol/ glycopyrronium/ mometasone (resolution of 4 February 2021)
- Beclometasone/ formoterol/ glycopyrronium (resolution of 5 August 2021)

Annex IV: Therapeutic information for omalizumab (resolution of 17 December 2015)
Annex XII / Annex IX: Definition of reference price groups fluticasone furoate/vilanterol
DMP guideline (DMP-RL): Asthma

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as 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".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

Against the background of the wording of the therapeutic indication (severe asthma), it is assumed that therapy with tezepelumab is only indicated in addition to high-dose inhaled corticosteroids (ICS) and at least one other medicinal product for maintenance treatment or, in children and adolescents, also in addition to medium-dose ICS and montelukast and a long-acting beta-2 -adrenergic receptor agonist (LABA) and a long-acting muscarinic receptor antagonist (LAMA).

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The medicinal stage scheme for children, adults and adolescents of the National Health Care Guideline Asthma (National Asthma Health Care Guideline 2020, 4th edition, version 1) should be taken into account. It is assumed that in the therapeutic indication of tezepelumab, patients in patient group a) are mapped to stages 5 to 6 of the medication-based stage scheme for children and adolescents and patients in patient group b) are mapped to stages 4 to 5 of the medication-based stage scheme for adults of the National Asthma Health Care Guideline 2020.

The guidelines recommend therapy with a LAMA in addition to high-dose ICS and LABA, both in stage 5 for children and adolescents and in stage 4 for adults. Tiotropium is approved from the group of LAMAs. The additional administration of tiotropium to ICS and LABA showed advantages in the area of morbidity. Another escalation option for children and adolescents (stage 6) and for adults (stage 5) is omalizumab in addition to high-dose ICS and LABA and LAMA, if necessary. Omalizumab may only be used as a possible appropriate comparator therapy in patients who fully meet the criteria of the marketing authorisation and the therapeutic indication for omalizumab. According to the product information, treatment with omalizumab "should only be considered in patients who can be presumed to have IgE (immunoglobulin E)-mediated asthma (see section 4.2)" Omalizumab is indicated in adolescents (12 years and older) and adults "as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and a reduced lung function (FEV1 < 80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist" (Product information Xolair(R), October 2021).

Long-term therapy with oral corticosteroids (OCS) is a lower-ranking alternative therapy for the treatment of severe asthma in children, adolescents and adults. In justified cases, the administration of OCS for the treatment of severe asthma is also possible. These should only be used for a short time and in the lowest effective dose. When treating asthma with OCS, it must be made sure that the dosage of OCS does not exceed the Cushing's threshold permanently, if possible. Treatment of exacerbations must be distinguished from this.

Due to its narrow therapeutic range, theophylline is not the substance of first choice in asthma therapy and is therefore not determined as an appropriate comparator therapy. Nevertheless, patients who receive theophylline as a concomitant medication in the present therapeutic indication can be included in the population relevant for the benefit assessment.

Montelukast is only approved as an adjunctive treatment in suffering from mild to moderate persistent asthma. Nevertheless, patients with severe asthma who receive Montelukast in the present therapeutic indication according to the recommendation of the National Asthma Health Care Guideline 2020 can be included in the relevant population for the benefit assessment.

The National Asthma Health Care Guideline recommends a therapy trial with mepolizumab, reslizumab, benralizumab or dupilumab in adults with severe

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eosinophilic asthma in stage 5. Similarly, for the active ingredients mepolizumab, reslizumab and benralizumab, a hint for a minor additional benefit was found in each case in a sub-population within the framework of the benefit assessment according to Section 35a SGB V. Against this background, the active ingredients mepolizumab, reslizumab, benralizumab or dupilumab (in addition to high-dose ICS and LABA and, if applicable, LAMA) are designated as part of the appropriate comparator therapy in adults, provided that the criteria necessary for the use of the respective antibodies are fulfilled. For children and adolescents, a therapy trial with mepolizumab (6 years of age and older) or dupilumab (12 years of age and older) is recommended in stage 6 according to National Asthma Health Care Guideline: However, as the evidence for both antibodies in this patient group is very limited, the recommendation is secondary to omalizumab. Against this background, the active ingredients mepolizumab or dupilumab (in addition to high-dose ICS and LABA and, if applicable, LAMA) are only named as an appropriate comparator therapy option for adolescents if the necessary criteria for the use of omalizumab are not met.

The marketing authorisations and product information for the medicinal product of the appropriate comparator therapy must be observed.

Patient-individual therapy refers to the selection of product classes, not to the selection of individual active ingredients within a product class.

The unchanged continuation of an inadequate therapy of severe asthma, if the option of therapy escalation still exists, does not correspond to an appropriate comparator therapy in case of uncontrolled severe asthma.

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

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

2.1.3 Extent and probability of the additional benefit

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

a) Adolescents 12 to 17 years with severe asthma who are inadequately controlled despite high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

An additional benefit is not proven.

b) Adults with severe asthma who are inadequately controlled despite high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

An additional benefit is not proven.

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Justification:

The pharmaceutical company considers the patient groups of adolescents (patient group a) and adults (patient group b) together and uses the NAVIGATOR, PATHWAY and DESTINATION studies for the assessment of the additional benefit.

NAVIGATOR study

The randomised, double-blind NAVIGATOR study enrolled 1061 patients aged 12 to 80 years with severe asthma who had ≥ 2 exacerbations of their disease within 12 months prior to screening, defined by treatment with systemic corticosteroids or hospitalisation or emergency department visit. In addition, all patients had to have been treated with medium or high-dose ICS and at least 1 other control medication in the last 3 months before screening. The patients were either treated with additional tezepelumab (N = 529) or received placebo (N = 532). All patients had to continue their initial asthma medication unchanged throughout the study. Adjustment of medication was not allowed. Similarly, biologic agents were not allowed to be used for treatment. The study enrolled a screening period of 5 to 6 weeks followed by a 52-week treatment phase. Following the treatment phase, patients were followed up for 12 weeks or could be included in the extension DESTINATION study. The primary endpoint of the NAVIGATOR study was the annual exacerbation rate.

The study was conducted between November 2017 and November 2020 in several study sites in Argentina, Australia, Austria, Brazil, Canada, France, Germany, Israel, Japan, South Korea, Russia, Saudi Arabia, South Africa, Taiwan, Ukraine, UK, USA and Vietnam.

PATHWAY study

The randomised, double-blind PATHWAY study enrolled 584 patients aged 18-75 years with severe asthma who had ≥ 2 deteriorations of their disease or 1 severe deterioration within 12 months before screening. Deterioration was defined as treatment with systemic corticosteroids for ≥ 3 days or emergency department visit or hospitalisation. Severe deterioration was defined as hospitalisation for ≥ 24 hours within 12 months prior to screening. In addition, all patients had to have been treated with medium or high-dose ICS and LABA for ≥ 6 months prior to screening. Patients were randomly assigned in a 1:1:1 ratio to treatment with tezepelumab at doses of 280 mg every 2 weeks (N = 137), 210 mg every 4 weeks (N = 137), 70 mg every 4 weeks (N = 138) or placebo (N = 138). 34 patients from a non-GCP-compliant (Good Clinical Practice) study centre were excluded from the analyses.

Treatment with tezepelumab at a dosage of 210 mg every 4 weeks is in accordance with the requirements of the product information. All patients should continue their initial asthma medication unchanged throughout the course of the study. However, changes in asthma medication were possible at the doctor's discretion and after consultation with the sponsor. The use of biologics was not allowed during the study. The PATHWAY study included a screening of 5 weeks followed by a 52-week treatment phase and a follow-up of 12 weeks. The primary endpoint of the study was the annual exacerbation rate.

The study was conducted between December 2013 and March 2017 in several study sites in the USA, Slovakia, Bulgaria, Czech Republic, Hungary, Israel, Japan, Latvia, Lithuania, Serbia, South Africa and Ukraine.

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DESTINATION study

The randomised, double-blind extension study DESTINATION enrolled patients who completed the NAVIGATOR study (N = 827) or the SOURCE study (N = 124). Patients who previously received tezepelumab were enrolled in the tezepelumab arm while maintaining blinding. Patients who previously received placebo were randomised in a 1:1 ratio to treatment with tezepelumab or placebo. The existing control medication could be reduced during the study at the doctor's discretion in case of stable symptomatology. In addition, exacerbations that occurred during the study should be treated appropriately. The use of biologics was not allowed.

The study included a 52-week treatment phase for patients from the NAVIGATOR study. These were followed up for 12 weeks after the treatment phase. The primary endpoint of the study was the incidence of adverse events and serious adverse events.

The study was conducted between January 2019 and October 2021 in several study sites in Argentina, Australia, Austria, Brazil, Canada, France, Germany, Israel, Poland, Russia, Saudi Arabia, South Korea, Taiwan, Turkey, USA, Ukraine and Vietnam.

From all 3 studies, the pharmaceutical company forms sub-populations of patients for whom - according to the pharmaceutical company - no therapy with a biologic agent of the appropriate comparator therapy is possible due to their individual biomarker status. Patients with a total immunoglobulin E value of <76 IU/mL or ≥1,500 IU/mL, an eosinophil count of <300 eosinophils/µL and a fractional exhaled nitric oxide (FeNO) value of <25 ppb were enrolled in these biomarker$_{low}$ populations. The sub-populations considered by the pharmaceutical company include 95 patients in the NAVIGATOR study (tezepelumab: n = 55; placebo: n = 40) and 21 patients in the PATHWAY study (tezepelumab: n = 12; placebo: n = 9). For the DESTINATION study, the pharmaceutical company additionally restricts the population to patients who were previously treated in the NAVIGATOR study. This sub-population comprises 64 patients (tezepelumab: n = 45; placebo: n = 19).

Based on these sub-populations, the pharmaceutical company conducted a meta-analysis with the NAVIGATOR and PATHWAY studies; the results of the extension study DESTINATION were presented separately.

In addition, the pharmaceutical company submits an adjusted indirect comparison with dupilumab via the bridge comparator placebo for the benefit assessment. On the intervention side, the pharmaceutical company includes the meta-analytically summarised modified intention-to-treat (mITT) population of the NAVIGATOR and PATHWAY studies, which comprises all patients of the ITT population corresponding to the approved therapeutic indication of tezepelumab. For the derivation of an additional benefit, the pharmaceutical company uses an indirect comparison with the QUEST study.

The QUEST study is a randomised, double-blind phase III study comparing dupilumab in 2 different doses with placebo. The study enrolled patients aged 12 years and older with

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uncontrolled, moderate-to-severe asthma who were already on existing therapy with moderate or high-dose ICS and 1 to 2 other control medications (e.g. LABA) in stable doses.

Suitability of the study for the benefit assessment

In the NAVIGATOR, PATHWAY and DESTINATION studies, the enrolled patients had inadequate asthma control despite their existing asthma therapy. However, in the respective control arms of the 3 studies, no therapy escalation was planned at the start of the study, while patients in the intervention arms received tezepelumab as an add-on therapy. The unchanged continuation of an inadequate therapy of severe asthma, if the option of therapy escalation still exists, does not correspond to an appropriate comparator therapy in case of uncontrolled asthma. Accordingly, the options for patient-individual therapy escalation according to the G-BA's appropriate comparator therapy should have been exhausted within the control arm of the respective study in order to adequately treat the patients' symptoms on the one hand and to present a suitable comparison between tezepelumab and the appropriate comparator therapy for the benefit assessment on the other.

The pharmaceutical company states that in relation to the biomarker$_{low}$ population, the continued previous treatment with high-dose ICS + LABA and, if applicable, LAMA would represent exhausted inhaled maintenance therapy. Therefore, no further therapy escalation would be considered for patients in these sub-populations and the continuation of the existing therapy would correspond to the G-BA's appropriate comparator therapy.

In the biomarker$_{low}$ population of the NAVIGATOR study, 73% (intervention arm) and 60% (placebo arm) and in the corresponding population of the PATHWAY study, 100% (intervention arm) and 89% (placebo arm) did not receive LAMA at the start of the study. However, the escalation option with a LAMA (tiotropium) is part of the appropriate comparator therapy determined by the G-BA and of the medicinal stage scheme for adults and adolescents of the National Asthma Health Care Guideline in case of inadequate asthma control in an already existing therapy with 2 control medications (e.g. ICS und LABA). The additional administration of LAMA also represents a therapy escalation option within the G-BA's appropriate comparator therapy for patients not eligible for biologic agents.

Initiation of a control medication with LAMA was not allowed during the treatment phase in the NAVIGATOR study. In the PATHWAY study and the DESTINATION extension study, adjustment of the control medication was possible according to the pharmaceutical company. In the context of the written and oral statements, the pharmaceutical company stated that an adjustment of the therapy with LAMA had not been made in any patient in the PATHWAY study and in 1.6% of the patients in the DESTINATION study. Information on whether and how many patients in the disease history had already received a therapy with LAMA that was not continued for certain reasons had not been collected in the 3 studies.

It therefore remains unclear for the vast majority of patients in the Biomarker$_{low}$ populations whether a therapy trial with LAMA would have been an appropriate and consequently necessary therapy escalation according to the G-BA's appropriate comparator therapy. There is no implementation of the appropriate comparator therapy in the biomarker$_{low}$. Accordingly,

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the results of the NAVIGATOR, PATHWAY and DESTINATION studies cannot be taken into account for the benefit assessment.

Suitability of the indirect comparison for the benefit assessment

In the presented adjusted indirect comparison of tezepelumab and dupilumab, all patients in the comparator arm received dupilumab. However, the pharmaceutical company does not state that dupilumab is the individually most suitable escalation therapy for the patients included in the QUEST study.

According to the medication staging scheme of the National Asthma Health Care Guideline, therapy with monoclonal antibodies is only indicated in adults if asthma control is not achieved with combination therapy with a maximum-dose ICS, a LABA and a LAMA. Likewise, the efficacy of the various possible treatment options of stage 5, which also includes combination therapy of ICS and LABA and LAMA, should be evaluated before escalating therapy to stage 6 (antibody administration) in adolescents. In the QUEST study, only 9% of patients in the dupilumab arm continued existing treatment with LAMA as a 2nd or 3rd control medication. Overall, LAMA was not available for escalation of existing therapy in the study. Furthermore, no data are available that document unsuitability of LAMA for the patients in the dupilumab arm of the QUEST study. It therefore remains unclear whether a therapy with dupilumab represents the adequate patient-individual therapy escalation (taking into account the previous therapy) for these patients. There is no implementation of the appropriate comparator therapy in the submitted indirect comparison of tezepelumab versus dupilumab. Accordingly, the adjusted indirect comparison of tezepelumab and dupilumab cannot be considered for the benefit assessment.

In summary, an additional benefit of tezepelumab compared with the appropriate comparator therapy is therefore not proven for patient group a (adolescents aged 12 to 17 years with severe asthma that is inadequately controlled despite high-dose ICS plus another medicinal product used for maintenance treatment) nor for patient group b (adults with severe asthma that is inadequately controlled despite high-dose ICS plus another medicinal product used for maintenance treatment).

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product "Tezspire" with the active ingredient tezepelumab. Tezepelumab is indicated as an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma who are inadequately controlled despite high dose inhaled corticosteroids plus another medicinal product for maintenance treatment. In the therapeutic indication to be considered, 2 patient groups were distinguished:

a) Adolescents 12 to 17 years with severe asthma who are inadequately controlled despite high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

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b) Adults with severe asthma who are inadequately controlled despite high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

The pharmaceutical company considers the patient groups of adolescents and adults together and uses the placebo-controlled NAVIGATOR, PATHWAY and DESTINATION RCT studies for the assessment of the additional benefit. From all 3 studies, the pharmaceutical company forms sub-populations (biomarker$_{low}$ population) of patients for whom, according to the pharmaceutical company, no therapy with a biologic agent of the appropriate comparator therapy is possible due to their individual biomarker status. However, it remains unclear for the vast majority of these patients whether a therapy trial with LAMA would have been a suitable and therefore necessary therapy escalation according to the G-BA's appropriate comparator therapy. In addition, the pharmaceutical company submits an adjusted indirect comparison with tezepelumab and dupilumab via the bridge comparator placebo for the benefit assessment. In the indirect comparison presented, however, it remains unclear whether therapy with dupilumab represents the adequate patient-individual therapy escalation (taking into account the previous therapy) for the patients in the comparator arm. There is no implementation of the appropriate comparator therapy in the biomarker$_{low}$ populations and in the submitted indirect comparison of tezepelumab versus dupilumab.

An additional benefit of tezepelumab compared to the appropriate comparator therapy is therefore not proven for both patient groups.

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

The number of patients is based on the target population in statutory health insurance (SHI). The resolution is based on the information from the dossier of the pharmaceutical company.

Overall, the information provided by the pharmaceutical company is largely plausible. Uncertainties in the determination of the respective percentages of patients with severe, uncontrolled asthma in Germany exist, among other things, due to the partial lack of medical confirmation or validation of self-reports of surveyed subjects, due to deviating or unclear operationalisation criteria and the partial exclusive consideration of criteria for adults.

No separate information was provided by the pharmaceutical company on the division of the target population into the patient groups named by the G-BA.

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 Tezspire (active ingredient: tezepelumab) at the following publicly accessible link (last access: 31 January 2023):

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

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Treatment with tezepelumab should only be initiated and monitored by doctors experienced in severe asthma therapy.

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: .15 April 2023).

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.

Since the inhaled corticosteroids (ICS) and the beta-2-adrenergic receptor agonists (LABA) and ICS + LABA are assigned to fixed combinations of a reference price group, one representative of each product class is shown as an example when deriving the costs.

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Patient population a)

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Tezepelumab	Continuously, 1 x every 28 days	13.0	1	13.0
Inhaled corticosteroids (ICS, high dose)				
Fluticasone	Continuously, 2 x daily	365.0	1	365.0
Long-acting beta-2-adrenergic receptor agonists (LABA)				
Formoterol	Continuously, 2 x daily	365.0	1	365.0
ICS + LABA fixed combinations (high-dose)				
Fluticasone | Salmeterol	Continuously, 2 x daily	365.0	1	365.0

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Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Long-acting muscarinic receptor antagonists (LAMA)				
Tiotropium	Continuously, 1 x daily	365.0	1	365.0
Appropriate comparator therapy				
Inhaled corticosteroids (ICS, high dose)				
Fluticasone	Continuously, 2 x daily	365.0	1	365.0
Long-acting beta-2-adrenergic receptor agonists (LABA)				
Formoterol	Continuously, 2 x daily	365.0	1	365.0
ICS + LABA fixed combinations (high-dose)				
Fluticasone | Salmeterol	Continuously, 2 x daily	365.0	1	365.0
Long-acting muscarinic receptor antagonists (LAMA)				
Tiotropium	Continuously, 1 x daily	365.0	1	365.0
Monoclonal antibodies				
Omalizumab	Continuously, 1 x every 28 days – Continuously, 1 x every 14 days	13.0 – 26.1	1	13.0 – 26.1
Mepolizumab	Continuously, 1 x every 28 days	13.0	1	13.0
Dupilumab	Continuously, 1 x every 14 days	26.1	1	26.1

Patient population b)

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Tezepelumab	Continuously, 1 x every 28 days	13.0	1	13.0
Inhaled corticosteroids (ICS, high dose)				

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Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Fluticasone	Continuously, 2 x daily	365.0	1	365.0
Long-acting beta-2-adrenergic receptor agonists (LABA)				
Formoterol	Continuously, 2 x daily	365.0	1	365.0
ICS + LABA fixed combinations (high-dose)				
Fluticasone | Salmeterol	Continuously, 2 x daily	365.0	1	365.0
Long-acting muscarinic receptor antagonists (LAMA)				
Tiotropium	Continuously, 1 x daily	365.0	1	365.0
ICS + LABA + LAMA fixed combinations (high-dose)				
Beclometasone | Formoterol | Glycopyrronium	Continuously, 2 x daily	365.0	1	365.0
Appropriate comparator therapy				
Inhaled corticosteroids (ICS, high dose)				
Fluticasone	Continuously, 2 x daily	365.0	1	365.0
Long-acting beta-2-adrenergic receptor agonists (LABA)				
Formoterol	Continuously, 2 x daily	365.0	1	365.0
ICS + LABA fixed combinations (high-dose)				
Fluticasone | Salmeterol	Continuously, 2 x daily	365.0	1	365.0
Long-acting muscarinic receptor antagonists (LAMA)				
Tiotropium	Continuously, 1 x daily	365.0	1	365.0
ICS + LABA + LAMA fixed combinations (high-dose)				
Beclometasone | Formoterol | Glycopyrronium	Continuously, 2 x daily	365.0	1	365.0
Monoclonal antibodies				
Omalizumab	Continuously, 1 x every 28 days – Continuously, 1 x every 14 days	13.0 – 26.1	1	13.0 – 26.1

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Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Mepolizumab	Continuously, 1 x every 28 days	13.0	1	13.0
Reslizumab	Continuously, 1 x every 28 days	13.0	1	13.0
Benralizumab	Continuously, 1 x every 56 days	6.5	1	6.5
Dupilumab	Continuously, 1 x every 14 days	26.1	1	26.1

Consumption:

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

For the inhaled corticosteroids and for the long-acting beta-2 receptor agonists, the highest regular dosage according to the product information was taken into account for daily consumption.

Since omalizumab is given according to baseline IgE levels and body weight, the range is from 150 mg every 4 weeks to 600 mg every 2 weeks.

The active ingredient reslizumab is administered according to body weight. For dosages depending on body weight, the average body measurements from the official representative statistics “Microcensus 2017 – body measurements of the population” were applied (average body weight: 77.0 kg).[2]

[2] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

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Patient population a)

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					
Tezepelumab	210 mg	210 mg	1 x 210 mg	13.0	13 x 210 mg
Inhaled corticosteroids (ICS, high dose)					
Fluticasone[3]	500 µg	1,000 µg	2 x 500 µg	365.0	730 x 500 µg
Long-acting beta-2-adrenergic receptor agonists (LABA)					
Formoterol	12 µg	24 µg	2 x 12 µg	365.0	730 x 12 µg
ICS + LABA fixed combinations (high-dose)					
Salmeterol | Fluticasone	50 µg / 250 µg	100 µg / 500 µg	2 x 50 µg / 250 µg	365.0	730 x 50 µg / 250 µg
Long-acting muscarinic receptor antagonists (LAMA)					
Tiotropium	5 µg	5 µg	2 x 2.5 µg	365.0	730 x 2.5 µg
Appropriate comparator therapy					
Inhaled corticosteroids (ICS, high dose)					
Fluticasone	500 µg	1,000 µg	2 x 500 µg	365.0	730 x 500 µg
Long-acting beta-2-adrenergic receptor agonists (LABA)					
Formoterol	12 µg	24 µg	2 x 12 µg	365.0	730 x 12 µg
ICS + LABA fixed combinations (high-dose)					
Salmeterol | Fluticasone	50 µg / 250 µg	100 µg / 500 µg	2 x 50 µg / 250 µg	365.0	730 x 50 µg / 250 µg
Long-acting muscarinic receptor antagonists (LAMA)					
Tiotropium	5 µg	5 µg	2 x 2.5 µg	365.0	730 x 2.5 µg
Monoclonal antibodies					
Omalizumab	150 mg – 600 mg	150 mg – 600 mg	1 x 150 mg – 4 x 150 mg	13.0 – 26.1	13 x 150 mg – 104.4 x 150 mg
Mepolizumab	100 mg	100 mg	1 x 100 mg	13.0	13 x 100 mg
Dupilumab	200 mg – 300 mg	200 mg – 300 mg	1 x 200 mg – 1 x 300 mg	26.1	26.1 x 200 mg – 26.1 x 300 mg

[3] The data refer to the recommended dosage for adolescents aged 16 to 17 years as an example

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Patient population b)

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					
Tezepelumab	210 mg	210 mg	1 x 210 mg	13.0	13 x 210 mg
Inhaled corticosteroids (ICS, high dose)					
Fluticasone	500 µg	1,000 µg	2 x 500 µg	365.0	730 x 500 µg
Long-acting beta-2-adrenergic receptor agonists (LABA)					
Formoterol	24 µg	48 µg	4 x 12 µg	365.0	1,460 x 12 µg
ICS + LABA fixed combinations (high-dose)					
Fluticasone | Salmeterol	500 µg /50 µg	1,000 µg /100 µg	4 x 250 µg / 25 µg	365.0	1,460 x 250 µg / 25 µg
Long-acting muscarinic receptor antagonists (LAMA)					
Tiotropium	5 µg	5 µg	2 x 2.5 µg	365.0	730 x 2.5 µg
ICS + LABA + LAMA fixed combinations (high-dose)					
Beclometasone | Formoterol | Glycopyrronium	344 µg/ 10 µg/18 µg	688 µg/20 µg/36 µg	4 x 172 µg/ 5 µg/9 µg	365.0	1460 x 172 µg/5 µg/9 µg
Appropriate comparator therapy					
Inhaled corticosteroids (ICS, high dose)					
Fluticasone	500 µg	1,000 µg	2 x 500 µg	365.0	730 x 500 µg
Long-acting beta-2-adrenergic receptor agonists (LABA)					
Formoterol	24 µg	48 µg	4 x 12 µg	365.0	1,460 x 12 µg
ICS + LABA fixed combinations (high-dose)					
Fluticasone | Salmeterol	500 µg /50 µg	1,000 µg /100 µg	4 x 250 µg / 25 µg	365.0	1,460 x 250 µg / 25 µg
Long-acting muscarinic receptor antagonists (LAMA)					
Tiotropium	5 µg	5 µg	2 x 2.5 µg	365.0	730 x 2.5 µg
ICS + LABA + LAMA fixed combinations (high-dose)					
Beclometasone | Formoterol | Glycopyrronium	344 µg/ 10 µg/18 µg	688 µg/20 µg/36 µg	4 x 172 µg/ 5 µg/9 µg	365.0	1460 x 172 µg/5 µg/9 µg
Monoclonal antibodies					
Omalizumab	150 mg – 600 mg	150 mg – 600 mg	1 x 150 mg – 4 x 150 mg	13.0 – 26.1	13 x 150 mg – 104.4 x 150 mg

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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
Mepolizumab	100 mg	100 mg	1 x 100 mg	13.0	13 x 100 mg
Reslizumab	225 mg	225 mg	2 x 100 mg + 1 x 25 mg	13.0	26 x 100 mg + 13 x 25 mg
Benralizumab	30 mg	30 mg	1 x 30 mg	6.5	6.5 x 30 mg
Dupilumab	200 mg – 300 mg	200 mg – 300 mg	1 x 200 mg – 1 x 300 mg	26.1	26.1 x 200 mg – 26.1 x 300 mg

Costs:

Costs of the medicinal products:

Patient population a)

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					
Tezepelumab 210 mg	3 IFE	€ 5,016.41	€ 2.00	€ 485.48	€ 4,528.93
Tiotropium 2.5 µg	180 SD	€ 197.83	€ 2.00	€ 17.70	€ 178.13
Fluticasone 500 µg[4]	120 SD	€ 45.52	€ 2.00	€ 2.71	€ 40.81
Formoterol 12 µg[4]	180 SD	€ 83.97	€ 2.00	€ 5.75	€ 76.22
Salmeterol 50 µg | Fluticasone 250 µg[4]	180 SD	€ 100.27	€ 2.00	€ 7.04	€ 91.23
Appropriate comparator therapy					
Tiotropium 2.5 µg	180 SD	€ 197.83	€ 2.00	€ 17.70	€ 178.13
Fluticasone 500 µg[4]	120 SD	€ 45.52	€ 2.00	€ 2.71	€ 40.81
Formoterol 12 µg[4]	180 SD	€ 83.97	€ 2.00	€ 5.75	€ 76.22
Salmeterol 50 µg | Fluticasone 250 µg[4]	180 SD	€ 100.27	€ 2.00	€ 7.04	€ 91.23
Omalizumab 150 mg	10 IFE	€ 5,173.05	€ 2.00	€ 500.82	€ 4,670.23
Mepolizumab 100 mg	3 SFI	€ 3,731.89	€ 2.00	€ 149.88	€ 3,580.01
Dupilumab 200 mg	6 SFI	€ 4,337.25	€ 2.00	€ 418.99	€ 3,916.26

[4] Fixed reimbursement rate

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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
Dupilumab 300 mg	6 SFI	€ 4,337.25	€ 2.00	€ 418.99	€ 3,916.26
Abbreviations: IFE = solution for injection in a pre-filled syringe, SD = single doses, TAB = tablets, SFI = solution for injection					

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Patient population b)

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Tezepelumab 210 mg	3 IFE	€ 5,016.41	€ 2.00	€ 485.48	€ 4,528.93
Fluticasone 500 µg[4]	120 SD	€ 45.52	€ 2.00	€ 2.71	€ 40.81
Tiotropium 2.5 µg	180 SD	€ 197.83	€ 2.00	€ 17.70	€ 178.13
Formoterol 12 µg[4]	180 SD	€ 83.97	€ 2.00	€ 5.75	€ 76.22
Salmeterol 25 µg | Fluticasone 250 µg[4]	360 SD	€ 147.33	€ 2.00	€ 10.76	€ 134.57
Beclometasone 172 µg | Formoterol 5 µg | Glycopyrronium 9 µg	360 SD	€ 268.49	€ 2.00	€ 24.41	€ 242.08
Appropriate comparator therapy					
Fluticasone 500 µg[4]	120 SD	€ 45.52	€ 2.00	€ 2.71	€ 40.81
Tiotropium 2.5 µg	180 SD	€ 197.83	€ 2.00	€ 17.70	€ 178.13
Formoterol 12 µg[4]	180 SD	€ 83.97	€ 2.00	€ 5.75	€ 76.22
Salmeterol 25 µg | Fluticasone 250 µg[4]	360 SD	€ 147.33	€ 2.00	€ 10.76	€ 134.57
Beclometasone 172 µg | Formoterol 5 µg | Glycopyrronium 9 µg	360 SD	€ 268.49	€ 2.00	€ 24.41	€ 242.08
Omalizumab 150 mg	10 IFE	€ 5,173.05	€ 2.00	€ 500.82	€ 4,670.23
Mepolizumab 100 mg	3 SFI	€ 3,731.89	€ 2.00	€ 149.88	€ 3,580.01
Reslizumab 100 mg	2 CIS	€ 1,180.99	€ 2.00	€ 111.02	€ 1,067.97
Reslizumab 25 mg	2 CIS	€ 303.72	€ 2.00	€ 27.76	€ 273.96
Benralizumab 30 mg	1 SFI	€ 2,606.22	€ 2.00	€ 249.52	€ 2,354.70
Dupilumab 200 mg	6 SFI	€ 4,337.25	€ 2.00	€ 418.99	€ 3,916.26
Dupilumab 300 mg	6 SFI	€ 4,337.25	€ 2.00	€ 418.99	€ 3,916.26
Abbreviations: IFE = solution for injection in a pre-filled syringe, SD = single doses, TAB = tablets, SFI = solution for injection, CIS = concentrate for the preparation of an infusion solution					

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Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Tezepelumab

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on

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the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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 12 October 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 14 November 2022, the pharmaceutical company submitted a dossier for the benefit assessment of tezepelumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 15 November 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient tezepelumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 February 2023, and the written statement procedure was initiated with publication on the G-BA website on 15 February 2023. The deadline for submitting statements was 9 March 2023.

The oral hearing was held on 27 March 2023.

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

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umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 3 May 2023, and the proposed resolution was approved.

At its session on 12 May 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	12 October 2022	Determination of the appropriate comparator therapy
Working group Section 35a	15 March 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	27 March 2023	Conduct of the oral hearing
Working group Section 35a	5 April 2023 26 April 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	3 May 2023	Concluding discussion of the draft resolution
Plenum	12 May 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 12 May 2023

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

Prof. Hecken

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