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
Dupilumab (new therapeutic indication: bronchial asthma, 6 to 11 years)

of 6 October 2022

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of 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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient dupilumab (Dupixent) was listed for the first time on 1 December 2017 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 4 April 2022, dupilumab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 14 April 2022, i.e. at the latest within four weeks after the notification of the pharmaceutical company of the approval of a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3,

number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient dupilumab with the new therapeutic indication (bronchial asthma, ≥ 6 to ≤ 11 years).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 July 2022 on the website of the G-BA (http://www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a decision on whether an additional benefit of dupilumab 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 addenda to the benefit assessment prepared by the 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 dupilumab.

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 Dupilumab (Dupixent) in accordance with the product information

Adults and adolescents

Dupixent is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), see section 5.1, who are inadequately controlled with high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

Children 6 to 11 years old

Dupixent is indicated in children 6 to 11 years old as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), see section 5.1, who are inadequately controlled with medium to high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

Therapeutic indication of the resolution (resolution of 6 October 2022):

Children 6 to 11 years old

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

Dupixent is indicated in children 6 to 11 years old as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), see section 5.1, who are inadequately controlled with medium to high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Children 6 to 11 years old with severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO) who are inadequately controlled with medium to high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment

Appropriate comparator therapy for dupilumab:

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

- high-dose ICS and LABA and, if necessary, 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

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. For children 6 to 11 years old with severe asthma, the following product classes and active ingredients are approved:

- Inhaled corticosteroids: Beclometasone, budesonide, fluticasone
- Systemic corticosteroids: Prednisolone, prednisone
- Beta-2-adrenergic receptor agonists (short, long-acting): Salbutamol, fenoterol, reproterol, salmeterol, formoterol, terbutaline, bambuterol, clenbuterol/ ambroxol
- Anticholinergics: Tiotropium bromide
- Other active ingredients: Theophylline, omalizumab, mepolizumab

On 2. A non-medicinal treatment at the expense of the SHI is unsuitable.

On 3. The following resolutions of the G-BA are available for the therapeutic indication of bronchial asthma:

- Mepolizumab (Annex XII – Benefit assessment according to Section 35a SGB V, resolution of 21 July 2016) *(adult patients with asthma*)
- Reslizumab (Annex XII – Benefit assessment according to Section 35a SGB V, resolution of 6 July 2017) *(adult patients with asthma*)
- Benralizumab (Annex XII – Benefit assessment according to Section 35a SGB V, resolution of 2 August 2018) *(adult patients with asthma*)
- Mepolizumab (Annex XII – Benefit assessment according to Section 35a SGB V, resolution of 22 March 2019)
- Dupilumab (Annex XII – Benefit assessment according to Section 35a SGB V, resolution of 20 February 2020) *(asthma patients ≥ 12 years)*
- Resolution of the G-BA on an amendment to the Pharmaceuticals Directive (AM-RL) - Annex IV: Therapeutic information for omalizumab (resolution of 17 December 2015)
- 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 indication according to Section 35a paragraph 7 SGB V (see “Information on Appropriate Comparator Therapy”). A statement was submitted by the AkdÄ.
The medicinal stage scheme for children and adolescents of the National Asthma Health Care Guideline (NVL Asthma, 4th edition, 2020, version 1) must be taken into account. It is assumed that in the therapeutic indication of dupilumab, patients are presented in stages 5 to 6 of the medicinal stage scheme for children and adolescents of the National Asthma Health Care Guideline 2020.

In view of the wording of the therapeutic indication (severe asthma), it is assumed that therapy with dupilumab is only indicated for children 6 to 11 years old in addition to high dose

inhaled corticosteroids and at least one other medicinal product for maintenance treatment or in addition to medium dose ICS and Montelukast and LABA and LAMA.
In stage 5 of the National Asthma Health Care Guideline, a combination of high dose ICS, LABA and LAMA is recommended in addition to treatment with high dose ICS and another controller. In stage 6 of the National Asthma Health Care Guideline, the administration of an anti-IgE antibody (omalizumab) or, secondary to the therapy with omalizumab, the administration of an anti-IL-5 antibody is recommended in addition to the medicinal treatment of stage 5. In its statement, the AkdÄ also refers to the specifications of the National Asthma Health Care Guideline, which stipulates the exhaustion of all options provided for in therapy stages IV and V, including a combination of these active ingredients. When considering the use of a biologic agent (stage 6), most experience in the present age group is with the monoclonal anti-IgE antibody omalizumab; the data basis for the anti-IL-5 antibody mepolizumab is still limited in childhood and adolescence.
Based on the available evidence, for children 6 to 11 years old with severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), who are inadequately controlled with high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment, the G-BA has determined a patient-individual therapy escalation as the appropriate comparator therapy, taking into account the prior therapy, selecting high dose ICS and LABA and possibly LAMA or high dose ICS and LABA and, if applicable, LAMA and omalizumab, provided that the criteria necessary for the application of omalizumab are fulfilled.

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 children 6 to < 12 years old "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 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 of Xolair®, July 2020).
Montelukast is only approved as an add-on treatment in patients 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.
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.
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.

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. If the therapeutic indication also includes patients for whom no further escalation of their existing inadequate therapy is possible, the dossier shall demonstrate for this patient population that no further therapy escalation is possible. Reasons should be given why patients are not eligible for the therapy escalations determined to be appropriate (e.g., omalizumab, tiotropium).

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 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 dupilumab is assessed as follows:

An additional benefit is not proven for the treatment of children 6 to 11 years old with severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO) who are inadequately controlled with medium to high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

Justification:

For the assessment of the additional benefit of dupilumab, the pharmaceutical company presents the randomised, double-blind VOYAGE study, in which 408 children 6 to 11 years old with uncontrolled moderate to severe asthma were treated in a 2:1 ratio with either dupilumab (N = 273) or placebo (N = 135). The study comprises a screening phase of 4 weeks, a treatment phase of 52 weeks and a follow-up phase of 12 weeks, provided that the patients did not participate in the subsequent open-label 1-year extension study. According to the inclusion criterion, all patients had been on maintenance treatment for ≥ 3 months with a stable dose for ≥ 1 month before screening with a medium or high dose inhaled corticosteroid (ICS) plus a 2nd control medication (long-acting beta-2-adrenergic receptor agonists [LABA], leukotriene receptor antagonist [LTRA], long-acting muscarinic receptor antagonist [LAMA] or methylxanthine) or monotherapy with a high dose ICS. For lack of asthma control, one of the following criteria had to be met during the 4-week screening: Asthma Control Questionnaire (ACQ)-5-IA score ≥ 1.5 on at least 1 day or application of on-demand medication on ≥ 3 days/week in at least 1 week or at least 1 nocturnal awakening due to asthma with need for

application of on-demand medication or asthma symptomatology on ≥ 3 days/week in at least 1 week. The enrolled patients also had an asthma deterioration within the last year with at least 1 treatment with systemic corticosteroids or a hospitalisation or emergency department visit.

The primary endpoint of the study was the annual rate of severe exacerbations. Secondary endpoints were assessed in the categories of morbidity, health-related quality of life and side effects. The study was conducted between April 2017 and August 2020 in Argentina, Australia, Brazil, Canada, Chile, Colombia, Hungary, Italy, Lithuania, Mexico, Poland, Russia, South Africa, Spain, Turkey, Ukraine and the USA.

In its dossier, the pharmaceutical company restricts the total population of the VOYAGE study to 350 patients with type 2 inflammation, defined as an eosinophil count ≥ 150/µl and/or an exhaled fraction of nitric oxide (FeNO) ≥ 20 ppb at the start of the study, in accordance with the marketing authorisation.

In the sub-population of the VOYAGE study presented by the pharmaceutical company, no child was treated with a LAMA or a monoclonal antibody at the time of enrolment in the study. Therefore, according to the definition of the National Asthma Health Care Guideline 2020, only children with a high ICS dose have severe asthma in this population at the start of the study. Since dupilumab is only indicated in addition to an ICS plus another medicinal product used for maintenance treatment, this results in a sub-population of 286 patients, which corresponds to the target population of the present benefit assessment. This corresponds to 81.7% (286/350) of the sub-population evaluated by the pharmaceutical company. For at least 80% of the patients in the sub-population of the VOYAGE study submitted by the pharmaceutical company, the inclusion criterion regarding the population for the present benefit assessment according to the therapeutic indication of dupilumab is fulfilled accordingly.

Suitability of the study for the benefit assessment

The patients in the VOYAGE study had uncontrolled asthma according to the inclusion criteria: In the sub-population evaluated by the pharmaceutical company, patients had 2.5 severe asthma exacerbations in the previous year, an ACQ-5-IA score of 2.2 at the start of the study and 2.5 inhalations of on-demand medication within 24 h at the start of the study (mean across both study arms)

However, in the control arm, no escalation of maintenance treatment was planned at the start of the study, while patients in the intervention arm received dupilumab as an add-on therapy. Also in the course of the study, no therapy escalation of the maintenance treatment was planned according to the protocol. Instead, patients should continue their existing maintenance treatment with a stable dose unchanged during the course of the study. Only after at least 2 severe asthma exacerbations could patients on high dose ICS monotherapy receive a 2nd control medication and patients on a combination of medium dose ICS and

another control medication are switched to a combination of high dose ICS and another control medication. Maintenance treatment consisting of > 2 control medications was not allowed at any point in the study.

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 study in order to adequately treat the patients' symptoms on the one hand and to present a suitable comparison between dupilumab and the appropriate comparator therapy for the benefit assessment on the other.

In the sub-population of the VOYAGE study presented by the pharmaceutical company, no child was treated with a LAMA at the time of enrolment in 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 children and adolescents of the National Asthma Health Care Guideline in case of inadequate asthma control in an already existing therapy with high dose ICS and another medicinal product. For children who have inadequate asthma control with a combination of medium dose ICS and another medicinal product, escalation to the combination of high dose ICS and another medicinal product is also an appropriate comparator therapy option.

Another option for therapy escalation is the administration of omalizumab in immunoglobulin E (IgE)-mediated asthma according to the appropriate comparator therapy defined by the G-BA, if the criteria of the marketing authorisation and the therapeutic information are completely fulfilled. Omalizumab was not allowed in the VOYAGE study within 130 days before screening and during the entire course of the study. It is not clear from the study documents whether the patients in the VOYAGE study ever received omalizumab before the start of the study. The pharmaceutical company determines the percentage of patients eligible for omalizumab to be 28.9% in the control arm of the sub-population it used.

In the written and oral statement procedure, the clinical experts expressed the opinion that the VOYAGE study should be taken into account. From a clinical point of view, it can be expected that the additional administration of tiotropium will lead to an improvement in lung function in only about 20% of the children in the therapeutic indication. Increasing the dose of a medium dose ICS to a high dose ICS would also only lead to an improvement in a small percentage of children, but would increase the rate of side effects. Similarly, only about 14% or 28.7% (depending on the version of the guideline) of the children in the study would have been eligible for omalizumab therapy.

In the VOYAGE study, however, the inadequate therapy was continued unchanged in the control arm at the start and during the course of the study in all children, although further options for therapy escalation existed according to the specific appropriate comparator therapy. Escalation of the existing maintenance treatment was not allowed at the start of the study or only possible during the course of the study after at least 2 severe asthma exacerbations for a small proportion of the study population. Accordingly, in the entire study

population of the VOYAGE study, no patient underwent escalation of the existing maintenance treatment.

It therefore remains unclear for how many patients in the study a therapy trial with LAMA, an increase in the ICS dose or a therapy trial with omalizumab would have been appropriate.

The therapy applied in the study in the control arm therefore does not correspond to the current recommendations for therapy escalation in the asthma treatment guidelines and also does not correspond to the appropriate comparator therapy of the G-BA. In the VOYAGE study, the appropriate comparator therapy of patient-individual therapy escalation is therefore not implemented.

In summary, the VOYAGE study results cannot be taken into account for the benefit assessment due to the high uncertainties regarding the implementation of the appropriate comparator therapy.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient dupilumab. The therapeutic indication assessed here is as follows: Add-on maintenance treatment in children 6 to 11 years old with severe asthma with type 2 inflammation who are inadequately controlled with medium to high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment. The G-BA determined a patient-individual therapy escalation as an appropriate comparator therapy, taking into account the prior therapy with the selection of high dose ICS and LABA and, if applicable, LAMA or high dose ICS and LABA and, if applicable, LAMA and omalizumab, provided that the criteria necessary for the administration of omalizumab are met. For the assessment of the additional benefit of dupilumab, the pharmaceutical company presents the randomised, double-blind VOYAGE study, in which children 6 to 11 years old with uncontrolled moderate to severe asthma were treated with either dupilumab or placebo.

In the VOYAGE study, the inadequate therapy was continued unchanged in the control arm at the start and during the course of the study in all children, although further options for therapy escalation existed according to the appropriate comparator therapy determined by the G-BA. Escalation of the existing maintenance treatment was not allowed at the start of the study or only possible during the course of the study after at least 2 severe asthma exacerbations for a small proportion of the study population. It therefore remains unclear for how many patients in the study a therapy trial with LAMA, an increase in the ICS dose or a therapy trial with omalizumab would have been appropriate. In summary, the VOYAGE study results cannot be taken into account for the benefit assessment due to the high uncertainties regarding the implementation of the appropriate comparator therapy. An additional benefit is therefore not proven.

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

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

The G-BA bases its resolution on the patient numbers from the dossier submitted by the pharmaceutical company.

The number given by the pharmaceutical company for the upper and lower limits is in a plausible order of magnitude, but is subject to uncertainty. In particular, it is unclear to what extent the methodological approach of the pharmaceutical company sufficiently comprehensively and specifically covered the patients in the therapeutic indication.

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 Dupixent (active ingredient: dupilumab) at the following publicly accessible link (last access: 22 July 2022):

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

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 September 2022).

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.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g., because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

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.

Since the inhaled corticosteroids (ICS) and the long-acting beta-2 receptor agonists (LABA) are assigned to 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 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.

According to the product information of dupilumab, doses depending on body weight are recommended for subcutaneous application in children from 6 to 11 years of age with asthma. 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] For the cost calculation, standard patients with an average body weight of 23.6 kg (for patients aged 6 to 7 years) and 42.1 kg (for patients aged 11 to 12 years) are considered.

For body weights between 15 kg to < 30 kg, treatment with dupilumab is recommended at 100 mg every 2 weeks or 300 mg every 4 weeks, and for body weights between 30 kg to < 60 kg at 200 mg every 2 weeks or 300 mg every 4 weeks. As dupilumab is not currently available in the 100 mg potency, children with a body weight between 15 kg to < 30 kg are only included in the table below using the approved dosage of 300 mg every 4 weeks.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Dupilumab 200 mg	1 x 14 days	26.1	1	26.1
Dupilumab 300 mg	1 x every 28 days	13	1	13
Inhaled corticosteroids (ICS, medium dose)				
Budesonide	2 x daily	365	1	365
Inhaled corticosteroids (ICS, high dose)				
Budesonide	2 x daily	365	1	365
Long-acting beta-2 receptor agonists (LABA)				
Formoterol	2 x daily	365	1	365

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

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	1 x daily	365	1	365
Appropriate comparator therapy				
high-dose ICS and LABA and, if necessary, LAMA or high-dose ICS and LABA and, if necessary, LAMA and omalizumab				
Inhaled corticosteroids (ICS, high dose)				
Budesonide	2 x daily	365	1	365
Long-acting beta-2 receptor agonists (LABA)				
Formoterol	2 x daily	365	1	365
Long-acting muscarinic receptor antagonists (LAMA)				
Tiotropium	1 x daily	365	1	365
Anti-IgE antibodies				
Omalizumab[3]	1 x every 14 - 28 days	13 – 26.1	1	13 – 26.1

Consumption:

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

For the inhaled corticosteroids, the highest regular dosage according to the product information was taken into account for daily consumption. For the active ingredient budesonide, a dosage of up to 800 µg per day may be indicated for children aged 6 to 11 years in severe cases of bronchial asthma. The cost calculation was based on a dosage of 800µg budesonide for high dose ICS and a dosage of 400 µg budesonide for medium dose ICS.

For the long-acting beta-2 receptor agonist formoterol, a dose of 12 µg twice daily is recommended for bronchial asthma for children 6 years and older.

Since omalizumab is given according to baseline IgE levels and body weight, the range is from 75 mg every 4 weeks to 600 mg every 2 weeks.

[3] According to the product information, omalizumab should only be considered in patients who can be presumed to have IgE (immunoglobulin E)-mediated asthma.

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					
Dupilumab 200 mg	200 mg	200 mg	200 mg	26.1	26.1 x 200 mg
Dupilumab 300 mg	300 mg	300 mg	300 mg	13	13 x 300 mg
Inhaled corticosteroids (ICS, medium dose)					
Budesonide 200 µg	200 µg	400 µg	2 x 200 µg	365	730 x 200 µg
Inhaled corticosteroids (ICS, high dose)					
Budesonide 400 µg	400 µg	800 µg	2 x 400 µg	365	730 x 400 µg
Long-acting beta-2 receptor agonists (LABA)					
Formoterol 12 µg	12 µg	24 µg	2 x 12 µg	365	730 x 12 µg
Long-acting muscarinic receptor antagonists (LAMA)					
Tiotropium 2.5 µg	5 µg	5 µg	2 x 2.5 µg	365	730 x 2.5 µg
Appropriate comparator therapy					
high-dose ICS and LABA and, if necessary, LAMA or high-dose ICS and LABA and, if necessary, LAMA and omalizumab					
Inhaled corticosteroids (ICS, high dose)					
Budesonide 400 µg	400 µg	800 µg	2 x 400 µg	365	730 x 400 µg
Long-acting beta-2 receptor agonists (LABA)					
Formoterol 12 µg	12 µg	24 µg	2 x 12 µg	365	730 x 12 µg
Long-acting muscarinic receptor antagonists (LAMA)					
Tiotropium 2.5 µg	5 µg	5 µg	2 x 2.5 µg	365	730 x 2.5 µg
Anti-IgE antibodies					
Omalizumab 75 and 150 mg	75 mg – 600 mg	75 mg – 600 mg	1 x 75 mg 4 x 150 mg	13 – 26.1	13 x 75 mg – 104.4 x 150 mg

Costs:

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					
Dupilumab 200 mg	6 SFI	€ 4,337.25	€ 1.77	€ 244.41	€ 4,091.07
Dupilumab 300 mg	6 SFI	€ 4,337.25	€ 1.77	€ 244.41	€ 4,091.07
Inhaled corticosteroids (ICS, medium dose)					
Budesonide[4] 200 µg	600 SD	€ 67.96	€ 1.77	€ 4.48	€ 61.71
Inhaled corticosteroids (ICS, high dose)					
Budesonide[4] 400 µg	300 SD	€ 63.83	€ 1.77	€ 4.16	€ 57.90
Long-acting beta-2 receptor agonists (LABA)					
Formoterol[4] 12 µg	180 SD	€ 83.97	€ 1.77	€ 5.75	€ 76.45
Long-acting muscarinic receptor antagonists (LAMA)					
Tiotropium 2.5 µg	180 SD	€ 197.83	€ 1.77	€ 10.33	€ 185.73
Appropriate comparator therapy					
high-dose ICS and LABA and, if necessary, LAMA or high-dose ICS and LABA and, if necessary, LAMA and omalizumab					
Inhaled corticosteroids (ICS, high dose)					
Budesonide[4] 400 µg	300 SD	€ 63.83	€ 1.77	€ 4.16	€ 57.90
Long-acting beta-2 receptor agonists (LABA)					
Formoterol[4] 12 µg	180 SD	€ 83.97	€ 1.77	€ 5.75	€ 76.45
Long-acting muscarinic receptor antagonists (LAMA)					
Tiotropium 2.5 µg	180 SD	€ 197.83	€ 1.77	€ 10.33	€ 185.73
Anti-IgE antibodies					
Omalizumab 75 mg	1 IFE	€ 281.54	€ 1.77	€ 14.96	€ 264.81
Omalizumab 150 mg	10 IFE	€ 5,173.05	€ 1.77	€ 292.14	€ 4,879.14

[4] Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Abbreviations: SD = single doses; IFE = solution for injection in a pre-filled syringe; SFI = solution for injection;					

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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 € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

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 11 May 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

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

By letter dated 19 April 2022 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 dupilumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 8 July 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 15 July 2022. The deadline for submitting written statements was 5 August 2022.

The oral hearing was held on 22 August 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.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 27 September 2022, and the proposed resolution was approved.

At its session on 06 October 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	11 May 2021	Determination of the appropriate comparator therapy
Working group Section 35a	17 August 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	22 August 2022	Conduct of the oral hearing
Working group Section 35a	31 August 2022; 14 September 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	27 September 2022	Concluding discussion of the draft resolution

Plenum	6 October 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 6 October 2022

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

Prof. Hecken