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: eosinophilic esophagitis, ≥ 1 year to < 12 years)

of 15 May 2025

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 all reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient 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 November 2024, 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, sentence 7).

On 28 November 2024, the pharmaceutical company has submitted a dossier 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 "Dupixent is indicated for the treatment of eosinophilic esophagitis in children 1 to 11 years old, weighing at least 15 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy" in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 3 March 2025 on the G-BA website (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 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 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

Dupixent is indicated for the treatment of eosinophilic esophagitis in children 1 to 11 years old, weighing at least 15 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy.

Therapeutic indication of the resolution (resolution of 15.05.2025):

See new therapeutic indication according to marketing authorisation.

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Children 1 to 11 years old with eosinophilic esophagitis (EoE), who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy

Appropriate comparator therapy for dupilumab:

An individualised therapy with a selection of budesonide and proton pump inhibitors (PPI)

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or

3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

On 1. Apart from dupilumab, no medicinal products are currently approved for the treatment of eosinophilic esophagitis (EoE) in children 1 to 11 years old.

On 2. Apart from endoscopic dilatation in severe, acute cases of disease in individual cases, non-medicinal therapy is not usually considered in the present therapeutic indication.

On 3. In the therapeutic indication under consideration here, no resolutions of the G-BA are available.

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present therapeutic indication.

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.

Overall, the reliable evidence on medicinal therapy options for the treatment of eosinophilic esophagitis (EoE) is limited, particularly in children. Based on the available evidence, recommendations can be derived for medicinal therapy with topical corticosteroids, which is presented as the most effective therapy, with proton pump inhibitors (PPI) as further medicinal therapy, as well as the recommendation for an elimination diet[2].

Apart from dupilumab, no medicinal products are currently approved for the treatment of EoE in children 1 to 11 years old. Budesonide, the active ingredient approved for use in adults, also does not have a marketing authorisation for use in children.

[2] Franciosi JP et al. Medical treatment of eosinophilic esophagitis. Cochrane Database of Systematic Reviews [online]. 2023(7):Cd004065. URL: http://dx.doi.org/10.1002/14651858.CD004065.pub4

The guidelines[3, 4, 5] uniformly make a strong recommendation for treatment with topical corticosteroids, both in children and adolescents as well as in adults. Of the topical corticosteroids, budesonide in particular has the most reliable evidence in the therapeutic indication, including for the treatment of EoE in paediatric populations[6, 7].

In addition to budesonide, PPI are also recommended in the guidelines for the treatment of paediatric patients.[3 - 5] Accordingly, treatment with PPI can induce remission of active EoE. There is evidence on the use of PPI for EoE, among others, from systematic reviews and meta-analyses[8, 9] as well as from individual studies[10, 11, 12].

In principle, the recommendation is that if an active EoE is detected, induction therapy should first be initiated as high-dose therapy with budesonide or PPI. The efficacy of any induction therapy should be closely evaluated clinically and via endoscopic-histological assessment after a period of 8 to 12 weeks. When a clinical and histological remission is achieved, the medicinal therapy should be continued at a lower dosage than the induction therapy as part of long-term maintenance treatment. In case of relapse, it is recommended to re-initiate induction therapy. In case of non-response, unless a clinical and histological remission is achieved, therapy should be switched. In individual cases of non-response and persistent histological activity, combination therapy of budesonide and PPI, possibly with dietary adherence may be indicated.

Individualised therapy with selection of budesonide and PPI as an appropriate comparator therapy is therefore considered appropriate. As part of individualised therapy, it is assumed that the children receive adequate treatment for eosinophilic esophagitis in accordance with guideline recommendations. Treatment with budesonide in accordance with the guideline recommendations may be indicated both in children who have not yet received budesonide therapy and in children who respond to budesonide therapy. Furthermore, adjustments to the therapies should be possible

[3] Lucendo AJ et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United European Gastroenterol J 2017;5(3):335-358

[4] Madisch A, Koop H, Miehlke S et al. S2k guideline Gastroesophageal reflux disease and eosinophilic esophagitis of the German Society for Gastroenterology, Digestive and Metabolic Diseases (DGVS) - AWMF registry number: 021–013. Z Gastroenterol 2023; 61(07): 862-933

[5] Dhar A et al. British Society of Gastroenterology (BSG) and British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) joint consensus guidelines on the diagnosis and management of eosinophilic oesophagitis in children and adults. Gut 2022;71(8):1459-1487

[6] Rawla P et al. Efficacy and safety of budesonide in the treatment of eosinophilic esophagitis: updated systematic review and meta-analysis of randomized and non-randomized studies. Drugs R D 2018;18(4):259-269.

[7] Munoz-Osores E et al. Corticosteroids for eosinophilic esophagitis in children: a meta-analysis. Paediatrics 2020;146(5)

[8] Lucendo AJ, et al. Efficacy of Proton Pump Inhibitor Drugs for Inducing Clinical and Histologic Remission in Patients With Symptomatic Esophageal Eosinophilia: A Systematic Review and Meta-Analysis. Clinical Gastroenterology and Hepatology 2016; 14: 13–22

[9] Tomizawa Y et al. Efficacy of Pharmacologic Therapy for Eosinophilic Esophagitis: A Systematic Review and Network Meta-Analysis. J Clin Gastroenterol 2018;52(7):596-606

[10] Gutierrez-Junquera C, et al. High prevalence of response to proton-pump inhibitor treatment in children with esophageal eosinophilia. J Paediatr Gastroenterol Nutr 2016; 62:704–710

[11] Laserna-Mendieta EJ, et al. Efficacy of proton pump inhibitor therapy for eosinophilic oesophagitis in 630 patients: results from the EoE connect registry. Aliment Pharmacol Ther 2020; 52: 798–807

[12] Gutiérrez-Junquera C et al. The Role of Proton Pump Inhibitors in the Management of Paediatric Eosinophilic Esophagitis. Frontiers in Paediatrics 2018: 62: 704–710

in both arms of a clinical study if the children under investigation require an adjustment to the therapy for the treatment of EoE.

In children 1 to 11 years old, the off-label use of budesonide and PPIs are two therapy options that have already been established in medical treatment and have proved to be effective and well tolerated in the treatment of EoE on the basis of evidence-based guideline recommendations[212] as well as experience from clinical practice. There are no approved therapy options for children 1 to 11 years old. Therefore, the use of unapproved therapy options is medically necessary for the patient population to be assessed. According to the generally recognised state of medical knowledge, the off-label use is considered the therapy standard in the therapeutic indication to be assessed. With the medicinal product to be assessed, a medicinal product approved in the therapeutic indication is available for the first time. In accordance with Section 6, paragraph 2, sentence 3, number 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), it is therefore appropriate to determine the off-label use of medicinal products as the appropriate comparator therapy for children 1 to 11 years old with EoE.

The determination of the off-label use of medicinal products as an appropriate comparator therapy by resolution on the benefit assessment according to Section 35a paragraph 3 SGB V does not affect the procedure according to Section 35c SGB V.

Endoscopic dilatation treatment is thought to be used sporadically in refractory cases and the presence of strictures. Endoscopic dilatation is therefore not considered a regular comparator, but should be offered for complications in both arms, for example.

If elimination diets or avoidance diets achieved reduction of symptoms, e.g. in the context of allergic reactions to certain foods, it is assumed that these will be continued. In view of the fact that permanent elimination diets go hand in hand with restrictions in a balanced diet that meets needs, elimination diets are not considered as the sole therapy.

In summary, an individualised therapy with selection of budesonide and PPI is determined as the appropriate comparator therapy for the present therapeutic indication of dupilumab for the treatment of children 1 to 11 years old. Individualised therapy is based on the assumption that several treatment options, which allow an individualised medical treatment decision, are available.

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

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.

Editorial note: The term "individualised therapy" is used instead of previously used terms such as "patient-individual therapy" or "therapy according to doctor's instructions". This harmonises the terms used in the European assessment procedures (EU-HTA).

2.1.3 Extent and probability of the additional benefit

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

Children 1 to 11 years old with eosinophilic esophagitis (EoE), who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy

An additional benefit is not proven.

Justification:

Submitted EE-1877 study

The EE-1877 study was presented for the assessment of the additional benefit of dupilumab for the treatment of eosinophilic esophagitis (EoE) in children 1 to 11 years old. The study consists of three parts. In study part A, a randomised, double-blind comparison of dupilumab versus placebo was conducted. The treatment duration in study part A was 16 weeks. Each of the study parts B and C included an extension phase in which all children were treated with dupilumab. Endpoints in the categories of mortality, morbidity, health-related quality of life and side effects were investigated.

Study population and study medication

For enrolment in the study, children had to have active EoE confirmed endoscopically by biopsy with a peak intraepithelial eosinophil count ≥ 15 eos/hpf[13] in at least one esophageal region. Another inclusion criterion was an inadequate response to previous treatment with proton pump inhibitors (PPI) for at least 8 weeks, which had to have taken place before the esophageal biopsy. The children also had to show symptoms of EoE. According to the exclusion criteria, no children who had been treated with topical corticosteroids (TCS) in the 8 weeks prior to randomisation were allowed to participate. Also excluded were children for whom therapy with PPI, leukotriene antagonists, nasal and/or inhaled corticosteroids had to be started, discontinued or the dosage regimen of this therapy had to be adjusted during this period. Children who had started or adapted an elimination diet 6 weeks prior to screening were also excluded.

An endoscopic biopsy at baseline was planned prior to randomisation. In addition, the children had the choice of continuing the PPI therapy unchanged from the screening phase in the further course of the study or discontinuing it. If an elimination diet was carried out, this had to be continued without any changes. The intake of TCS (for swallowing) and systemic corticosteroids was not permitted. Systemic corticosteroids and/or TCS could only be taken as emergency medication, e. g. to treat intolerable EoE symptoms. An esophageal dilatation could also be performed in an emergency.

Part A of the study comprised three arms: two dupilumab arms, at a lower and higher dose respectively, and a placebo arm. A total of 102 children were randomised in a 1:1:1 ratio to the lower-dose dupilumab arm (31 children), the higher-dose dupilumab arm (37 children) and the placebo arm (34 children). Only the dosage regimen for the weight class ≥ 15 kg to < 30 kg in the higher-dose dupilumab arm corresponds to the dosage according to the product

[13] eos/hpf: Eosinophils per high resolution visual field

information. All other dosage regimens deviate from the requirements in the product information for dupilumab.

Comparator therapy and suitability for the early benefit assessment

An individualised therapy with selection of budesonide and PPI was determined as the appropriate comparator therapy for the present indication.

In part A of the EE-1877 study, the children enrolled were treated with either dupilumab or placebo. Medicinal therapy for the treatment of EoE was only possible with limitations. TCS and thus also budesonide, which is named as a therapy option of the appropriate comparator therapy, were not permitted in the 8 weeks prior to the start of the study and during the entire duration of the study. Therapy with TCS could only be initiated in exceptional cases as part of emergency therapy. Although 62 % of the children in the comparator arm had received budesonide in the past, the percentage of children who had responded inadequately to TCS or had an intolerance or contraindication was only 44 %. This means that these criteria were not met for more than half of the study population, so that the use of budesonide would at least have been an option for a considerable percentage of the children in the placebo arm.

Treatment with PPI, which was also named as a component of the appropriate comparator therapy, was also limited. This is because only a few children could be treated with PPI in the study if they had decided to continue treatment with PPI and continued their existing PPI therapy unchanged from the screening phase. According to the study protocol, it was not permitted to adjust the dose of PPI therapy during the study or to restart or discontinue PPI therapy. As a result, only 32 % of the children in the comparator arm on placebo continued their PPI therapy without further adjustment; the remaining 68% received only placebo and thus, no other medicinal therapy for the treatment of EoE.

In the overall assessment, it was noted that the appropriate comparator therapy was not implemented in the EE-1877 study. Treatment with budenoside was not carried out in any of the children in the comparator arm. Treatment with PPI was only possible to a limited extent. According to the guidelines, PPI are recommended as high-dose therapy in addition to budesonide. After 8 to 12 weeks, the efficacy should be re-evaluated and the therapy changed if there is no response. Accordingly, children receiving PPI as primary therapy who have not achieved sufficient clinical and histological remission should be switched to therapy with budesonide. In certain cases, a combination therapy can be indicated, if applicable. Consequently, continuation of inadequate therapy is not in line with guideline recommendations. Overall, the procedure in the study based on the fact that budesonide was not regularly available for all children and that treatment with PPI was only possible to a limited extent and no adjustments were permitted, is considered inappropriate. Thus, the children in the comparator arm did not receive adequate treatment for eosinophilic esophagitis in accordance with guideline recommendations.

In addition, a comparable treatment duration of 16 weeks alone is insufficient to assess long-term effects of dupilumab on the treatment of EoE in children. Due to the chronic inflammatory course of the disease, children with EoE depend on long-term therapy. Thus, no statements can be derived on the additional benefit of dupilumab compared to the appropriate comparator therapy on the basis of the study presented.

Furthermore, it should be noted that the treatment with administration of dupilumab in the population relevant for the benefit assessment in the higher-dose dupilumab arm was partly inadequate, as a potentially relevant percentage of children were not treated according to the requirements in the product information and thus, not in compliance with the marketing authorisation.

Conclusion of the EE-1877 study

In summary, the EE-1877 study is not suitable for the assessment of the additional benefit of dupilumab compared with the appropriate comparator therapy, an individualised therapy with selection of budesonide and PPI. It is determined that the therapy in the comparator arm was inadequate. On the one hand, the regular use of budesonide was not possible. On the other, treatment with PPIs was only permitted with limitations. The appropriate comparator therapy was therefore not implemented. An additional benefit is correspondingly not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of the medicinal product Dupixent with the active ingredient dupilumab in a new therapeutic indication "Treatment of eosinophilic esophagitis in children 1 to 11 years old, weighing at least 15 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy".

The G-BA determined the appropriate comparator therapy to be an individualised therapy with selection of budesonide and proton pump inhibitors (PPI).

The pharmaceutical company submits the study EE-1877. In part A of the study, dupilumab was compared with placebo over a period of 16 weeks in children who had previously responded inadequately to PPI. In the overall assessment, it was noted that the appropriate comparator therapy was not implemented in the EE-1877 study. Treatment with budenoside was not carried out in any of the children in the comparator arm. Treatment with PPI was only possible to a limited extent. The procedure in the study therefore does not correspond to the implementation of the appropriate comparator therapy. In addition, the comparable treatment duration of 16 weeks alone is insufficient to assess long-term effects of dupilumab on the treatment of EoE in children. Furthermore, a potentially relevant percentage of children were not treated in accordance with the requirements in the product information and thus, not in compliance with the marketing authorisation.

In summary, no statements can be derived on the additional benefit of dupilumab compared to the appropriate comparator therapy on the basis of the data presented. 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 (SHI).

The resolution is based on the patient numbers stated in the pharmaceutical company's dossier. Due to various uncertainty factors[14] in determining the patient numbers, the information on the SHI target population is subject to uncertainties overall. It can be assumed that the percentage of children with an inadequate response to conventional medicinal therapy is significantly higher than estimated by the pharmaceutical company, despite the existing uncertainties. However, the lower limit is subject to uncertainty despite the underestimation of the percentage value, since the prevalence rate in Germany in the age group relevant here may also be lower. An underestimation of the SHI target population can be assumed for the upper limit.

[14] IQWiG dossier assessment Dupilumab, eosinophilic esophagitis, 1 to 11 years from 26.02.2025

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: 7 April 2025):

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

Treatment with dupilumab should only be initiated and monitored by doctors experienced in treating patients with EoE.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 April 2025).

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) 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.

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.

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

As it is not always possible to achieve the exact calculated dose per day with the commercially available dosage strengths, in these cases rounding up or down to the next higher or lower available dose that can be achieved with the commercially available dose potencies as well as the scalability of the respective dosage form.

Dupilumab is approved for the indication of eosinophilic esophagitis in children one year and older with a body weight of at least 15 kg. For active ingredients that are dosed depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population"[15] are used as a basis.

The average body weight of 1-year-old children is 11.6 kg. The minimum weight of 15 kg according to the marketing authorisation of dupilumab is found in the 2017 microcensus in the age group of 2 to < 3-year-old children. The average body weight of children aged 5 to < 6 years is 20.8 kg. The average body weight of 6-year-olds is 23.6 kg and 11-year-olds is 42.1 kg.

In this particular patient population, it is up to the physician to decide which is the most appropriate dosage form for the respective child from 2 to < 6 years of age, depending on

[15] Federal health reporting. Average body measurements of the population (2017, both sexes, 1 year and older), www.gbe-bund.de

body weight and dose. For this reason, where available, the dosages of both a solid (tablet) and a liquid formulation (solution or suspension) are shown for each active ingredient.

Budesonide

Budesonide is approved only for patients 18 years and older. For the calculation of treatment costs in adolescents below 12 years of age, the recommended dosages according to the European guideline[16] are taken into account. Accordingly, the recommended daily dose for maintenance treatment in patients under 12 years of age is 1 mg of budesonide.

Proton pump inhibitors (PPI)

PPIs are not approved for use in patients with EoE. For the cost calculation in the context of the off-label use of PPIs for the treatment of EoE, the G-BA uses the evidence-based recommendations of the European[3] and the German guideline[4], from which dosage information for the use of omeprazole and esomeprazole can be derived[8, 9, 10, 11, 12].

Omeprazole and esomeprazole are the two proton pump inhibitors that are available in an age-appropriate dosage form.

In principle, the recommendations for remission-maintaining therapy, which refer to the once-daily administration of PPIs as standard doses and are generally lower than the doses of induction therapy, are used as the basis for the cost representation as long-term therapy.

Children 1 to 11 years old with eosinophilic esophagitis (EoE), who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ child/ year	Treatment duration/ treatment (days)	Treatment days/ child/ year
Medicinal product to be assessed				
Dupilumab	Continuously, 1 x every 7 days to 1 x every 14 days	26.1 – 52.1	1.0	26.1 – 52.1
Appropriate comparator therapy				
Individualised therapy with selection of budesonide and proton pump inhibitors (PPI)				
Budesonide	Continuously, 2 x daily	365.0	1.0	365.0
Esomeprazole	Continuously, 1 x daily	365.0	1.0	365.0
Omeprazole	Continuously, 1 x daily	365.0	1.0	365.0

[16] Lucendo AJ et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United European Gastroenterol J 2017;5(3):335-358; Supplementary Material: table 6; https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1177%2F2050640616689525&file=ueg2bf00698-sup-0001.pdf [accessed on 04.04.2025]

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ child/ treatment days	Consumption by potency/ treatment day	Treatment days/ Child/ year	Average annual consumption by potency
Medicinal product to be assessed					
Dupilumab	**Children with a body weight of 15 kg to < 30 kg**				
	200 mg	200 mg	1 x 200 mg	26.1	26.1 x 200 mg
	Children with a body weight of 40 kg to < 30 kg				
	300 mg	300 mg	1 x 300 mg	52.1	52.1 x 300 mg
Appropriate comparator therapy					
Individualised therapy with selection of budesonide and proton pump inhibitors (PPI)					
Budesonide	0.5 mg	1 mg	2 x 0.5 mg	365.0	730 x 0.5 mg
Esomeprazole (ECG 10 mg)	Children 1 year and older (15 kg body weight) to < 6 years				
	1 mg/kg 15 mg – 20.8 mg	15 mg = 22.5 ml 20.0 mg = 30 ml	2 x 10 mg	365.0	730 x 10 mg
Esomeprazole (ECT 20 mg)	Children 1 year and older (15 kg body weight) to < 6 years				
	1 mg/kg 20 mg	20 mg	1 x 20 mg	365.0	365 x 20 mg
Esomeprazole (ECT 40 mg)	Children aged 11 years and below				
	1 mg/kg 40 mg	40 mg	1 x 40 mg	365.0	365 x 40 mg
Omeprazole (POS suspension 2 mg/ml)	Children 1 year and older (15 kg body weight) to < 6 years				
	1 mg/kg 15 mg – 20.8 mg	15 mg – 20.8 mg	1 x 7.5 ml = 15 mg – 1 x 10.4 ml = 20.8 mg	365.0	2,737.5 ml = 365 x 7.5 ml – 3796 ml = 365 x 10.4 ml
Omeprazole (ECT 20 mg)	Children 1 year and older (15 kg body weight) to < 6 years				
	1 mg/kg 20 mg	20 mg	1 x 20 mg	365.0	365 x 20 mg
Omeprazole (ECT 40 mg)	Children aged 11 years and below				
	1 mg/kg 40 mg	40 mg	1 x 40 mg	365.0	365 x 40 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates

in accordance with Sections 130 and 130 a 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. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

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	€ 3,908.39	€ 1.77	€ 219.92	€ 3,686.70
Dupilumab 300 mg	6 SFI	€ 3,908.39	€ 1.77	€ 219.92	€ 3,686.70
Appropriate comparator therapy					
Budesonide 0.5 mg	100 ODT	€ 406.90	€ 1.77	€ 21.90	€ 383.23
Esomeprazole 10 mg	28 ECG	€ 53.45	€ 1.77	€ 2.33	€ 49.35
Esomeprazole 20 mg[17]	90 ECT	€ 19.67	€ 1.77	€ 0.66	€ 17.24
Esomeprazole 40 mg[17]	90 ECT	€ 23.81	€ 1.77	€ 0.99	€ 21.05
Omeprazole 2 mg	75 POS	€ 119.99	€ 1.77	€ 5.16	€ 113.06
Omeprazole 20 mg[17]	100 ECT	€ 22.22	€ 1.77	€ 0.86	€ 19.59
Omeprazole 40 mg[17]	100 ECT	€ 26.47	€ 1.77	€ 1.20	€ 23.50
Abbreviations: ECG = enteric coated granules; SFI = solution for injection; POS = powder for oral suspension; ODT = orally disintegrating tablet; ECT = enteric coated tablets					

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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 need to be taken into account.

[17] Fixed reimbursement rate

2.5 Designation of 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 the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates 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 the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or

- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same

combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Children 1 to 11 years old with eosinophilic esophagitis (EoE), who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.
References:
Product information for dupilumab (Dupixent); Dupixent® 200 mg solution for injection in a pre-filled syringe; last revised: November 2024.

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 their session on 10 October 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 28 November 2024, 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 1 VerfO.

By letter dated 29 November 2024 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 27 February 2025, and the written statement procedure was initiated with publication on the G-BA website on 3 March 2025. The deadline for submitting statements was 24 March 2025.

The oral hearing was held on 7 April 2025.

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 6 May 2025, and the proposed draft resolution was approved.

At their session on 15 May 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	10 October 2023	Determination of the appropriate comparator therapy
Working group Section 35a	2 April 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	7 April 2025	Conduct of the oral hearing
Working group Section 35a	16 April 2025 30 April 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	6 May 2025	Concluding discussion of the draft resolution
Plenum	15 May 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 15 May 2025

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

Prof. Hecken