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 oesophagitis, ≥ 12 years, min. 40 kg)

of 21 September 2023

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 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 7 October 2022, the pharmaceutical company submitted an application for postponement of the date for the start of the benefit assessment procedure for dupilumab, among others, in the present therapeutic indication "Treatment of eosinophilic oesophagitis in adults and adolescents 12 years and older" in accordance with Section 35a, paragraph 5b SGB V. The pharmaceutical company expected marketing authorisation extensions for the active ingredient dupilumab within the period specified in Section 35a paragraph 5b SGB V for multiple therapeutic indications at different times.

At its session on 17 November 2022, the G-BA approved the application to postpone the relevant date in accordance with Section 35a, paragraph 5b SGB V and postponed the relevant date for the start of the benefit assessment and the submission of a dossier for the benefit assessment for the therapeutic indication in question here to four weeks after the marketing authorisation of the last therapeutic indication of the therapeutic indications covered by the application, at the latest six months after the first relevant date. All marketing authorisations

for the therapeutic indications covered by the application according to Section 35a, paragraph 5b SGB V were granted within the 6-month period.

For the therapeutic indication in question here "Treatment of eosinophilic oesophagitis in adults and adolescents 12 years and older", dupilumab received the extension of the marketing authorisation as a major type 2 variation as defined according to Annex 2 No. 2 letter a to Regulation (EC) No. 1234/2008 of the Commission from 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 23 January 2023. In accordance with the resolution of 17 November 2022, the benefit assessment of the active ingredient dupilumab in this new therapeutic indication thus began at the latest within four weeks after the last marketing authorisation of dupilumab on 15 March 2023 in the therapeutic indications for the treatment of "Treatment of severe atopic dermatitis in children 6 months to 5 years of age", i.e. at the latest on 12 April 2023.

On 29 March 2023, the pharmaceutical company has submitted in due time a dossier in accordance with Section 4, paragraph 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient dupilumab with the new therapeutic indication "Treatment of eosinophilic oesophagitis in adults and adolescents 12 years and older".

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 03.07.2023 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

Based on 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, the G-BA decided on the question on whether an additional benefit of dupilumab compared with the appropriate comparator therapy could be determined – Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V. 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 IQWiG [1] according to the General Methods was not used in the benefit assessment of dupilumab – Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V.

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

Eosinophilic oesophagitis (EoE)

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

Dupixent is indicated for the treatment of eosinophilic oesophagitis in adults and adolescents 12 years and older, weighing at least 40 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy (see Section 5.1).

Therapeutic indication of the resolution (resolution of 21.09.2023):

See the approved therapeutic indication.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults and adolescents 12 years and older with eosinophilic oesophagitis (EoE), who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy

Appropriate comparator therapy for dupilumab:

- Therapy according to doctor's instructions, selecting budesonide as well as proton pump inhibitors (PPI)

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 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. Budesonide, along with dupilumab, is explicitly approved for the treatment of eosinophilic oesophagitis (EoE) in adults. For children and adolescents under 18 years of age with EoE, no medicinal products other than dupilumab have been approved so far.

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

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

Overall, the robust evidence on medicinal therapy options in the present therapeutic indication is limited. 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.

Besides dupilumab, only budesonide has so far been explicitly approved for the treatment of eosinophilic oesophagitis (EoE) in adults. In adolescents aged 12 years and older, in contrast, no medicinal products other than dupilumab have been approved so far. The active ingredients mentioned in the therapy recommendations, topical corticosteroids and proton pump inhibitors are also not approved for the treatment of children and adolescents with EoE.

The guidelines[2, 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 robust evidence in the therapeutic indication, including for the treatment of EoE in paediatric populations.[6, 7, 8, 9]

In addition to budesonide, PPIs are also recommended in the guidelines.[-5] According to these, treatment with PPIs can induce remission of active EoE in adults and adolescents. There is evidence on the use of PPIs in EoE from systematic reviews and meta-analyses, among others[10, 11, 12] as well as individual studies[13, 14, 15, 16].

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 as well as endoscopically and histologically after a period of 6 or 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.

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

[3] Hirano I, et al. AGA institute and the joint task force on allergy-immunology practice parameters clinical guidelines for the management of eosinophilic oesophagitis. Ann Allergy Asthma Immunol 2020;124(5):416-423

[4] Rank MA et al. Technical review on the management of eosinophilic oesophagitis: a report from the AGA institute and the joint task force on allergy-immunology practice parameters. Ann Allergy Asthma Immunol 2020;124(5):424-440.e417

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

[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] Hao LX et al. A meta-analysis of efficacy of topical steroids in eosinophilic esophagitis: From the perspective of histologic, clinical, and endoscopic outcome. Gastroenterol Hepatol 2021;44(4):251-260.

[9] de Heer J, Miehlke S, et al. Histologic and Clinical Effects of Different Topical Corticosteroids for Eosinophilic Esophagitis: Lessons from an updated meta-analysis of placebo-controlled randomised trials. Digestion 2020; 102: 377–385

[10] 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

[11] 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.

[12] Rokkas T et al. A network meta-analysis of randomized controlled trials on the treatment of eosinophilic esophagitis in adults and children J Clin Gastroenterol 2020

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

[14] Gómez-Torrijos, E et al. The efficacy of step-down therapy in adult patients with proton pump inhibitor-responsive oesophageal eosinophilia. Aliment Pharmacol Ther 2016, 43: 534-540

[15] 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

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

Adolescents 12 to < 18 years

In adolescents, the off-label use of budesonide and PPIs are two treatment options that have already been established in the treatment of adolescents[6–16] Guideline recommendations[2–5] and clinical experience have shown them to be effective and well tolerated in the treatment of EoE. For adolescents, apart from the medicinal product to be assessed here, no other approved therapeutic alternative is available, Section 6, paragraph 2, sentence 3, number 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV). Therefore, it is appropriate to determine the off-label use of medicinal products as the appropriate comparator therapy for this patient population.

Adults

Budesonide is an approved therapeutic alternative that is considered part of the therapy standard for the treatment of adults with EoE. According to the guideline recommendations, if no remission has been achieved after 6 or 8 to 12 weeks of treatment with budesonide, the therapy should be changed. Accordingly, a therapy attempt with PPI should be made. For certain patients, remission can be achieved with combination therapy of budesonide and PPI. Overall, treatment with budesonide and the off-label use of PPIs in adults are two established treatment options, which have proven to be effective and well tolerated for the treatment of EoE, based on evidence-based[6–16] Guideline recommendations[2–5] as well as from experience in clinical practice. In this context, the off-label use of PPIs is possible according to the generally recognised state of medical knowledge for the (relevant) group of patients who have not achieved satisfactory control of disease activity through treatment with budesonide alone. If treatment with budesonide as the only therapy for EoE does not lead to remission or if budesonide is not an option for medical reasons, therapy with PPI should be undertaken. In these cases, the use of PPIs is generally preferable to budesonide for this relevant patient group, Section 6, paragraph 2, sentence 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV). Therefore, it is appropriate to determine the off-label use of medicinal products as the appropriate comparator therapy for this patient population.

On the basis of the generally recognised state of medical knowledge, the underlying evidence-based[6–16] Guideline recommendations[2–5] and taking into account the experience from clinical practice in the treatment of adults and adolescents with EoE, the appropriate comparator therapy is determined to be a therapy according to doctor's instructions, selecting budesonide and PPI.

It is assumed that patients receive adequate treatment of eosinophilic oesophagitis in accordance with guideline recommendations as part of their therapy.

If the patients enrolled should also include patients who have not yet received therapy with budesonide, or also those who respond to therapy with budesonide, it can be assumed that treatment with budesonide can be suitable for these subjects in accordance with the guideline recommendations.

Any therapy adjustment required by the patients for the treatment of eosinophilic oesophagitis should be possible in both arms of a clinical study.

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.

Change of the appropriate comparator therapy

For adolescents 12 years and older as well as adults with eosinophilic oesophagitis (EoE), who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy, a therapy according to doctor's instructions was originally determined as the appropriate comparator therapy. In this context, budesonide and proton pump inhibitors (PPI) were possible comparators that could be considered in the context of a therapy according to doctor's instructions. Budesonide is approved for the treatment of EoE in adults, but not in minors. PPIs have not yet received a marketing authorisation for use in the treatment of eosinophilic oesophagitis. As a result of the ruling of the BSG of 22.02.2023 (file ref.: B 3 KR 14/21 R), the medicinal products recommended in the guidelines or used in healthcare, which do not have a marketing authorisation for the present indication or not an explicit one, cannot be generally considered as appropriate comparator therapy in the narrower sense within the meaning of Section 2, paragraph 1, sentence 3, Section 12 SGB V. Consequently, shortly after the start of the procedure in April 2023, the appropriate comparator therapy was changed. Two patient populations were considered: a) adults with EoE who are still eligible for treatment with budesonide because they have not yet received budesonide, with budesonide designated as the appropriate comparator therapy, and b) adults and adolescents with EoE who are not candidates for conventional medicinal therapy, for whom best supportive care was designated as the appropriate comparator therapy.

With the entry into force of the Act to Combat Supply Bottlenecks for Off-Patent Medicinal Products and to Improve the Supply of Paediatric Medicinal Products (ALBVVG) in July 2023, the Ordinance on the Benefit Assessment of Pharmaceuticals was amended so that, if the prerequisites specified in Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) are met, the off-label use of medicinal products as an appropriate comparator therapy can be determined again by way of exception. The change in the appropriate comparator therapy is indicated due to the amendment to the law.

In summary, the G-BA considers it appropriate to change the appropriate comparator therapy. In the present indication, the appropriate comparator therapy for the total population is a therapy according to doctor's instructions, selecting budesonide and proton pump inhibitors (PPI).

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.

2.1.3 Extent and probability of the additional benefit

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

Adults and adolescents 12 years and older with eosinophilic oesophagitis (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 study EE-1774

The multi-part study EE-1774 was submitted for the assessment of the additional benefit of dupilumab for the treatment of eosinophilic oesophagitis (EoE). Both study parts A and B have a similar randomised, controlled, double-blind study design and were conducted in parallel. Study part C is an open-label extension study following study parts A or B, in which only dupilumab was administered for 28 weeks. Study part C is not relevant for the early benefit assessment.

Adults and adolescents 12 years and older diagnosed with EoE by oesophageal biopsy with a peak intraepithelial eosinophil count of ≥ 15 eos/hpf[17] in at least 2 of 3 oesophageal regions were enrolled. In addition, swallowing difficulties had to be present on at least 4 episodes in the last 2 weeks before baseline and a DSQ[18] score of ≥ 10. Another inclusion criterion was failure to respond to a previous 8-week therapy with high-dose PPI, which had to have occurred before the biopsy. Unless high-dose PPI therapy had been administered in the past, participants were required to follow up with such therapy during the 12-week screening period and prior to baseline oesophageal biopsy.

According to the elimination criteria, no patients were allowed to participate in the study if they had received oral topical corticosteroids, including budesonide or fluticasone in the last 8 weeks before baseline.

During the double-blind controlled phase, the adults and adolescents in the study received either dupilumab or placebo for a treatment period of 24 weeks. In study part A, participants were randomised in a 1:1 ratio to the treatment arms 300 mg dupilumab versus placebo once a week each. In study part B, in addition to the treatment arms dupilumab versus placebo as in part A, an additional treatment arm with 300 mg dupilumab every fortnight was investigated, but this does not comply with the product information and is therefore not relevant. Following the treatment phase, participants were followed up for a period of 12 weeks.

The study investigated endpoints in the categories of mortality, morbidity, health-related quality of life and side effects, including the co-primary endpoints "percentage of patients with a peak of ≤ 6 eos/hpf" and "change in DSQ score".

Comparator therapy and suitability for the early benefit assessment

The enrolled adults and adolescents were treated with dupilumab in the intervention arm, while they received placebo in the comparator arm. Medicinal therapy for the treatment of EoE was only possible with restrictions for certain patients. Thus, as background therapy in both arms, participants who were treated with high-dose PPI, nasal and/or inhaled

[17] eos/hpf: Eosinophils per high resolution visual field
[18] DSQ: Dysphagia Symptom Questionnaire

corticosteroids or leukotriene antagonists as a stable treatment regimen during screening were allowed to continue this therapy unchanged throughout the study period. A regular adaptation of the therapy to the respective needs of the patients was not planned. 69% of patients received high-dose PPI therapy during screening, which they had to continue for the entire duration of the study. As a result, 31% did not have access to PPI.

Treatment with topical corticosteroids (TCS), including budesonide, was not allowed in the last 8 weeks before baseline and during the entire study duration. Only in exceptional cases could emergency therapy be initiated, consisting of systemic corticosteroids, TCS or oesophageal dilatation.

The appropriate comparator therapy was determined to be a therapy according to doctor's instructions, selecting budesonide and PPI. It is assumed here that patients receive adequate treatment for eosinophilic oesophagitis according to the guideline recommendations. According to the guidelines, PPIs are recommended as high-dose therapy in addition to budesonide for the treatment of EoE. However, the therapy efficacy should usually be reassessed after 6 or 8 to 12 weeks and if there is no response, change of therapy is recommended. Accordingly, patients receiving PPI as primary therapy who have not achieved sufficient clinical and histological remission should be switched to therapy with budesonide. For certain patients, combination therapy may be indicated. In any case, continuation of inadequate therapy is not in line with guideline recommendations. Accordingly, the procedure in the study that budesonide was not regularly available for all patients and the fact that participants who failed PPI in the screening period had to continue their PPI therapy unchanged throughout the study are considered inappropriate.

Conclusion of the study EE-1774

Overall, the study EE-1774 is unsuitable for the assessment of the additional benefit of dupilumab compared to the appropriate comparator therapy determined by the G-BA, therapy according to doctor's instructions, selecting of budesonide and PPI. The appropriate comparator therapy was not implemented due to the questionable therapy in the comparator arm, which did not allow budesonide to be regularly available to all patients, and in view of the high-dose PPI therapy performed during the entire duration of the study, without unrestricted adjustments to the medicinal therapy for the treatment of EoE being possible. An additional benefit is correspondingly not proven.

2.1.4 Summary of the assessment

This is the early benefit assessment of the medicinal product Dupixent with the active ingredient dupilumab in a new therapeutic indication "Treatment of eosinophilic oesophagitis in adults and adolescents 12 years and older 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 a therapy according to doctor's instructions, selecting budesonide as well as proton pump inhibitors (PPI).

The pharmaceutical company submits the study EE-1774. Parts A and B of the study compared dupilumab versus placebo in adults and adolescents who had previously failed therapy with high-dose PPI. Budesonide was not allowed to be regularly available to all patients. In addition, participants who failed screening for PPIs had to continue their high-dose PPI therapy unchanged throughout the study. The remaining participants did not have access to PPI. The procedure in the study neither corresponds to the appropriate comparator therapy nor to the guideline recommendations for the treatment of EoE.

In summary, no statements can be made on the additional benefit of dupilumab compared to the appropriate comparator therapy on the basis of the study presented. An additional benefit is 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).

Overall, the pharmaceutical company's information on the number of patients assigned to the target population is fraught with uncertainties. Taking into account the disease definition, a potentially deviating prevalence rate is to be output. On the one hand, the pharmaceutical company restricts to two instead of at least one product class(es) for the criterion of an insufficient response in the context of conventional medicinal therapy. On the other, the transferability of the percentage values for insufficient response to the current medical treatment situation is questionable.[19]

Nevertheless, despite the uncertainties described above, the G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier.

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 August 2023):

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 2023).

For the presentation of the costs, one year is assumed for all medicinal products.

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 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

[19] IQWiG's dossier assessment dupilumab, eosinophilic oesophagitis of 28.06.2023 (A23-23)

treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Budesonide

Budesonide is approved only for patients 18 years and older. For the calculation of treatment costs in adolescents 12 years and older, the recommended dosages according to the European guideline[20] are taken into account. Accordingly, the recommended daily dose for maintenance treatment in patients under 18 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[21] and the German guideline[22], from which dosage information for the use of omeprazole, esoprazole, pantoprazole, rabeprazole and lansoprazole in adults and minors can be derived[23, 24, 25, 26, 27].

No relevant studies on the use of dexlansoprazole in EoE were identified. For this reason, the costs for dexlansoprazole are not presented.

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. The doses tested differently in the studies are taken into account by specifying a range.

Dosages in adolescents 12 years and older[28] are within the range considered.[21-27]

The presentation of the costs of a time-limited induction therapy or high-dose PPI therapy, which corresponds to twice the standard dosage (twice daily administration), is omitted.

[20] 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 07.09.2023]*

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

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

[23] 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

[24] 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

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

[26] Gómez-Torrijos, E et al. The efficacy of step-down therapy in adult patients with proton pump inhibitor-responsive oesophageal eosinophilia. Aliment Pharmacol Ther 2016, 43: 534-540

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

[28] usually 1 to 2 mg/kg body weight once daily; however, the dose should not exceed the standard dose *(40 mg omeprazole, 40 mg esomeprazole, 40 mg pantoprazole, 20 mg rabeprazole, 30 mg lansoprazole, each once daily)*.

Adults and adolescents 12 years and older with eosinophilic oesophagitis (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/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Dupilumab	Continuously, 1 x every 7 days	52.1	1	52.1
Appropriate comparator therapy				
Therapy according to doctor's instructions, selecting budesonide and proton pump inhibitors (PPI)				
Budesonide	Continuously, 2 x daily	365	1	365.0
Proton pump inhibitors (PPI)				
Budesonide	Continuously, 1 x daily	365	1	365.0
Omeprazole	Continuously, 1 x daily	365	1	365.0
Esomeprazole	Continuously, 1 x daily	365	1	365.0
Pantoprazole	Continuously, 1 x daily	365	1	365.0
Rabeprazole	Continuously, 1 x daily	365	1	365.0
Lansoprazole	Continuously, 1 x daily	365	1	365.0

Consumption:

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	300 mg	300 mg	1 x 300 mg	52.1	52.1 x 300 mg
Appropriate comparator therapy					
Therapy according to doctor's instructions, selecting budesonide and proton pump inhibitors (PPI)					
Budesonide	0.5 mg - 1 mg	1 mg - 2 mg	2 x 0.5 mg - 2 x 1 mg	365.0	730 x 0.5 mg - 730 x 1 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Omeprazole	20 mg - 40 mg	20 mg - 40 mg	1 x 20 mg - 1 x 40 mg	365.0	365 x 20 mg – 365 x 40 mg
Esomeprazole	20 mg - 40 mg	20 mg - 40 mg	1 x 20 mg - 1 x 40 mg	365.0	365 x 20 mg – 365 x 40 mg
Pantoprazole	20 mg - 40 mg	20 mg - 40 mg	1 x 20 mg - 1 x 40 mg	365.0	365 x 20 mg – 365 x 40 mg
Rabeprazole	10 mg - 20 mg	10 mg - 20 mg	1 x 10 mg - 1 x 20 mg	365.0	365 x 10 mg – 365 x 20 mg
Lansoprazole	15 mg - 30 mg	15 mg - 30 mg	1 x 15 mg - 1 x 30 mg	365.0	365 x 15 mg – 365 x 30 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 300 mg	6 SFI	€ 3,990.65	€ 2.00	€ 385.05	€ 3,603.60
Appropriate comparator therapy					
Budesonide 0.5 mg	100 ODT	€ 448.26	€ 2.00	€ 158.18	€ 288.08
Budesonide 1 mg	100 ODT	€ 549.82	€ 2.00	€ 51.11	€ 496.71
Esomeprazole 20 mg[29]	90 ECH	€ 19.67	€ 2.00	€ 0.66	€ 17.01
Esomeprazole 40 mg[29]	90 ECH	€ 23.81	€ 2.00	€ 0.99	€ 20.82
Lansoprazole 15 mg[29]	98 ECC	€ 20.49	€ 2.00	€ 0.73	€ 17.76
Lansoprazole 30 mg[29]	98 ECC	€ 24.49	€ 2.00	€ 1.04	€ 21.45
Omeprazole 20 mg[29]	100 ECH	€ 22.22	€ 2.00	€ 0.86	€ 19.36
Omeprazole 40 mg[29]	100 ECH	€ 26.47	€ 2.00	€ 1.20	€ 23.27
Pantoprazole 20 mg[29]	100 ECT	€ 20.69	€ 2.00	€ 0.74	€ 17.95
Pantoprazole 40 mg[29]	100 ECT	€ 25.37	€ 2.00	€ 1.11	€ 22.26
Rabeprazole 10 mg[29]	98 ECT	€ 20.49	€ 2.00	€ 0.73	€ 17.76
Rabeprazole 20 mg[29]	98 ECT	€ 23.91	€ 2.00	€ 1.00	€ 20.91
Abbreviations: MRC, hard = modified release hard capsules; ECH = enteric-coated hard capsules; SFI = solution for injection; ECC = enteric-coated capsules; ODT = melting tablets; ECT = enteric-coated tablets;					

[29] Fixed reimbursement rate

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.

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.

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

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

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 10 May 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 13 April 2023.

On 29 March 2023, 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 VerfO.

By letter dated 31 March 2023 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 28 June 2023, and the written statement procedure was initiated with publication on the G-BA website on 3 July 2023. The deadline for submitting statements was 24 July 2023.

The oral hearing was held on 8 August 2023.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI 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 12 September 2023, and the proposed resolution was approved.

At its session on 21 September 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	10 May 2022	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	13 April 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	1 August 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	8 August 2023	Conduct of the oral hearing

Working group Section 35a	15 August 2023 5 September 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	12 September 2023	Concluding discussion of the draft resolution
Plenum	21 September 2023	Adoption of the resolution on the amendment of the AM-RL

Berlin, 21 September 2023

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

Prof. Hecken