Dupilumab (eosinophilic oesophagitis)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
DSQ	Dysphagia Symptom Questionnaire
EoE	eosinophilic oesophagitis
eos	eosinophils
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
hpf	high power field
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PPI	proton pump inhibitor
Q2W	every 2 weeks
QW	once weekly
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TCS	topical corticosteroids

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug dupilumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 30 March 2023.

Research question

The aim of this report is to assess the added benefit of dupilumab compared with the appropriate comparator therapy (ACT) in adults and adolescents 12 years and older, weighing at least 40 kg, with eosinophilic oesophagitis (EoE), who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy.

The research questions shown in Table 2 are derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of dupilumab

Research question	Therapeutic indication	ACT[a]
1	Adults with EoE who are still candidates for treatment with budesonide because they have not yet received budesonide[b]	Budesonide
2	Adults and adolescents with EoE, 12 years and older, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy[c]	BSC[d, e]

a. Presented is the respective ACT specified by the G-BA.
b. Adults who have not received prior treatment with budesonide and who are also not candidates for treatment with budesonide fall under research question 2.
c. According to the S2k guideline, conventional medicinal therapy includes topical corticosteroids and proton pump inhibitors [1].
d. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. Symptomatic treatment of heartburn or reflux symptoms with proton pump inhibitors may be indicated in the present therapeutic indication. Endoscopic dilatation treatment is assumed to be used sporadically in refractory cases and the presence of strictures. If elimination diets or avoidance diets achieved symptom reduction, e.g. in the context of allergic reactions to certain foods, it is assumed that these diets are continued.
e. In the present case, the drugs recommended in guidelines or used in clinical practice, that have no or no explicit approval for the present therapeutic indication, cannot be considered as ACT in the narrower sense within the meaning of §2 para 1 S. 3, §12 SGB V (BSG judgment of 22 February 2023, reference number: B 3 KR 14/21 R).

BSC: best supportive care; BSG: Federal Social Court; EoE: eosinophilic oesophagitis; G-BA: Federal Joint Committee; SGB: Social Code Book

On 13 April 2023, 2 months after the company submitted the dossier (30 March 2023), the G-BA modified the ACT as shown in Table 2. The original ACT of 10 May 2022 for the entire

population was treatment of physician's choice with budesonide and proton pump inhibitors (PPIs) as possible comparators. The company claimed to have followed the ACT specified by the G-BA. The information provided by the company in the dossier relates to the original ACT, however.

The present assessment is based on the adjusted ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks are used for the derivation of added benefit.

Since no suitable data are available for either of the 2 research questions designated by the G-BA, the assessment below is performed in a joint section of the report.

Results

No relevant study was identified from the check of the information retrieval.

The company, in contrast, identified the EE-1774 study and used study parts A and B of this study for the assessment of the added benefit of dupilumab. The data of the EE-1774 study presented by the company are unsuitable for drawing conclusions on the added benefit of dupilumab in comparison with the ACT. This is justified below.

Evidence presented by the company – EE-1774 study

The EE-1774 study consists of 3 parts: Study parts A and B presented by the company in the dossier are randomized, double-blind studies comparing dupilumab with placebo. Study part C is an open-label extension study in which patients who had completed study parts A or B received dupilumab for 28 weeks. The company excluded study part C from the assessment, as it does not allow a comparison with the ACT.

Study parts A and B included patients 12 years and older, weighing ≥ 40 kg, with a documented diagnosis of EoE. All study participants had baseline endoscopic biopsies with a demonstration of ≥ 15 intraepithelial eosinophils (eos) per high power field (hpf) in at least 2 of 3 oesophageal regions (proximal, mid, or distal). Patients also had to have a baseline Dysphagia Symptom Questionnaire (DSQ) score ≥ 10 and at least 4 episodes of dysphagia in the 2 weeks prior to baseline. Furthermore, the patients had to have already failed an 8-week high-dose PPI therapy before the start of the study.

After a 12-week screening phase, the patients received either dupilumab or matching placebo for 24 weeks. In study part A (N = 81), patients were randomized in a 1:1 ratio to treatment with dupilumab (300 mg once weekly, QW) or placebo. In study part B (N = 240), patients were randomized in a 1:1:1 ratio to treatment with dupilumab (300 mg once weekly, QW),

dupilumab (300 mg every 2 weeks, Q2W), or placebo. In the QW arm, dupilumab was administered as specified in the Summary of Product Characteristics (SPC). The dosage in the dupilumab Q2W arm, however, was not in compliance with the approval and is therefore not relevant for the present benefit assessment.

Patients on a stable dose of PPIs, nasal or inhaled corticosteroids, or leukotriene antagonists at screening were to continue these treatments unchanged throughout the study period.

Co-primary outcomes of the study were the proportion of patients achieving peak eosinophil count of ≤ 6 eos/hpf at week 24 and the change in DSQ total score from baseline to week 24.

Appropriate comparator therapy not implemented in the EE-1774 study

Research question 1 covers adult patients in the therapeutic indication who are still candidates for treatment with budesonide because they have not yet received budesonide. The G-BA specified budesonide as the ACT for this research question. In study parts A and B of the EE-1774 study, treatment with topical corticosteroids (TCS), including budesonide, was not allowed within 8 weeks prior to baseline, as well as during the entire study duration. The use of TCS was only possible as rescue treatment. Furthermore, there is no exact information on how many patients in the EE-1774 study had already received budesonide in the past. In the dossier, the company only provided the number of patients with prior TCS therapy (74% in the placebo arm versus 69% in the dupilumab arm), but this number included both budesonide and fluticasone. In principle, however, regular treatment with budesonide was not planned in the EE-1774 study according to the study protocol, which is why this study – irrespective of the question of whether a subpopulation of the study can be delimited for research question 1 – is not suitable for answering this research question.

Research question 2 covers patients who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy. The ACT for this patient population as defined by the G-BA is best supportive care (BSC). In its notes on the ACT, the G-BA pointed out that PPIs may be indicated for the symptomatic treatment of heartburn or reflux symptoms.

In addition to the above-mentioned restrictions of the background treatment with TCS, treatment with PPIs was also restricted in study EE-1774. Patients receiving high-dose PPI therapy during the screening phase had to continue treatment for the entire study duration without dose adjustment. All other patients were not allowed to start treatment with PPIs during the study. As a result, about 31% of the included patients did not have access to PPIs for symptom relief. The remaining patients (69%) received high-dose PPI therapy during screening, which they had to continue for the entire period of the study. A dose reduction was not allowed. However, high-dose PPI therapy is not a symptomatic treatment in the sense of the ACT. According to the SPCs, PPIs for the symptomatic treatment of reflux symptoms should

be used in lower doses and for a shorter treatment period than was the case in the study. Thus, according to the study protocol, no adequate symptomatic treatment with PPIs was possible for the patients in the EE-1774 study.

The ACT BSC was not implemented in the presented study parts A and B of study EE-1774. Thus, no suitable data are available to answer research question 2, irrespective of the question of whether a subpopulation can be delimited for research question 2.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of dupilumab in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 shows a summary of probability and extent of the added benefit of dupilumab.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [2,3].

Table 3: Dupilumab – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT[a]**	**Probability and extent of added benefit**
1	Adults with EoE who are still candidates for treatment with budesonide because they have not yet received budesonide[b]	Budesonide	Added benefit not proven
2	Adults and adolescents with EoE, 12 years and older, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy[c]	BSC[d, e]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. Adults who have not received prior treatment with budesonide and who are also not candidates for treatment with budesonide fall under research question 2.
c. According to the S2k guideline, conventional medicinal therapy includes topical corticosteroids and proton pump inhibitors [1].
d. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. Symptomatic treatment of heartburn or reflux symptoms with proton pump inhibitors may be indicated in the present therapeutic indication. Endoscopic dilatation treatment is assumed to be used sporadically in refractory cases and the presence of strictures. If elimination diets or avoidance diets achieved symptom reduction, e.g. in the context of allergic reactions to certain foods, it is assumed that these diets are continued.
e. In the present case, the drugs recommended in guidelines or used in clinical practice, that have no or no explicit approval for the present therapeutic indication, cannot be considered as ACT in the narrower sense within the meaning of §2 para 1 S. 3, §12 SGB V (BSG judgment of 22 February 2023, reference number: B 3 KR 14/21 R).

BSC: best supportive care; BSG: Federal Social Court; EoE: eosinophilic oesophagitis; G-BA: Federal Joint Committee; SGB: Social Code Book

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of dupilumab compared with the ACT in adults and adolescents 12 years and older, weighing at least 40 kg, with EoE, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy.

The research questions shown in Table 4 are derived from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of dupilumab

Research question	Therapeutic indication	ACT[a]
1	Adults with EoE who are still candidates for treatment with budesonide because they have not yet received budesonide[b]	Budesonide
2	Adults and adolescents with EoE, 12 years and older, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy[c]	BSC[d, e]

a. Presented is the respective ACT specified by the G-BA.
b. Adults who have not received prior treatment with budesonide and who are also not candidates for treatment with budesonide fall under research question 2.
c. According to the S2k guideline, conventional medicinal therapy includes topical corticosteroids and proton pump inhibitors [1].
d. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. Symptomatic treatment of heartburn or reflux symptoms with proton pump inhibitors may be indicated in the present therapeutic indication. Endoscopic dilatation treatment is assumed to be used sporadically in refractory cases and the presence of strictures. If elimination diets or avoidance diets achieved symptom reduction, e.g. in the context of allergic reactions to certain foods, it is assumed that these diets are continued.
e. In the present case, the drugs recommended in guidelines or used in clinical practice, that have no or no explicit approval for the present therapeutic indication, cannot be considered as ACT in the narrower sense within the meaning of §2 para 1 S. 3, §12 SGB V (BSG judgment of 22 February 2023, reference number: B 3 KR 14/21 R).

BSC: best supportive care; BSG: Federal Social Court; EoE: eosinophilic oesophagitis; G-BA: Federal Joint Committee; SGB: Social Code Book

On 13 April 2023, 2 months after the company submitted the dossier (30 March 2023), the G-BA modified the ACT as shown in Table 4. The original ACT of 10 May 2022 for the entire population was treatment of physician's choice with budesonide and PPIs as possible comparators. The company claimed to have followed the ACT specified by the G-BA. The information provided by the company in the dossier relates to the original ACT, however.

The present assessment is based on the adjusted ACT.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

Since no suitable data are available for either of the 2 research questions designated by the G-BA, the assessment below is performed in a joint section of the report.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on dupilumab (status: 17 January 2023)
- bibliographical literature search on dupilumab (last search on 17 January 2023)
- search in trial registries/trial results databases for studies on dupilumab (last search on 17 January 2023)
- search on the G-BA website for dupilumab (last search on 17 January 2023)

To check the completeness of the study pool:

- search in trial registries for studies on dupilumab (last search on 20 April 2023); for search strategies, see I Appendix A of the full dossier assessment

No relevant study was identified from the check.

The company, in contrast, identified the EE-1774 study [4] and used study parts A and B for the assessment of the added benefit of dupilumab. The data of the EE-1774 study presented by the company are unsuitable for drawing conclusions on the added benefit of dupilumab in comparison with the ACT. This is justified below.

Evidence presented by the company – EE-1774 study

The randomized EE-1774 study consists of 3 parts: Study parts A and B presented by the company in the dossier are randomized, double-blind studies comparing dupilumab with placebo. Study part C is an open-label extension study in which patients who had completed study parts A or B received dupilumab for 28 weeks. The company excluded study part C from the assessment, as it does not allow a comparison with the ACT.

Study parts A and B included patients 12 years and older, weighing ≥ 40 kg, with a documented diagnosis of EoE. All study participants had baseline endoscopic biopsies with a demonstration of ≥ 15 intraepithelial eos/hpf in at least 2 of 3 oesophageal regions (proximal, mid, or distal). Patients also had to have a baseline DSQ score ≥ 10 and at least 4 episodes of dysphagia in the 2 weeks prior to baseline. Furthermore, the patients had to have already failed an 8-week high-dose PPI therapy before the start of the study. Patients who had not had such therapy in the past had to undergo this treatment during the screening phase of the study and before their baseline oesophageal biopsy.

After a 12-week screening phase, the patients received either dupilumab or matching placebo for 24 weeks. In study part A (N = 81), patients were randomly assigned in a ratio of 1:1 to the following treatment arms:

- placebo, once weekly
- dupilumab, 300 mg QW

In study part B (N = 240), patients were randomly assigned in a ratio of 1:1:1 to the following treatment arms:

- placebo, once weekly
- dupilumab, 300 mg QW
- dupilumab, 300 mg Q2W

Randomization of patients in study parts A and B was stratified by age group (12 to 17 years; ≥ 18 years) and use of PPIs at randomization (yes; no).

In the QW arm, dupilumab was administered as specified in the SPC [5]. The dosage in the dupilumab Q2W arm, however, was not in compliance with the approval and is therefore not relevant for the present benefit assessment. This concurs with the company's assessment. Patients on a stable dose of PPIs, nasal or inhaled corticosteroids, or leukotriene antagonists at screening were to continue these treatments unchanged throughout the study period. The treatment phase was followed by a 12-week follow-up observation.

Co-primary outcomes of the study were the proportion of patients achieving peak eosinophil count of ≤ 6 eos/hpf at week 24 and the change in DSQ total score from baseline to week 24. Secondary patient-relevant outcomes were outcomes on morbidity, health-related quality of life, and adverse events (AEs).

The company presented the results of the study parts both individually and in the form of a meta-analysis. For the meta-analysis, it only considered the results of patients who were treated in compliance with the approved dosage.

Appropriate comparator therapy not implemented in the EE-1774 study

The G-BA divided the therapeutic indications into 2 research questions depending on the patients' pretreatment.

Research question 1 covers adult patients in the therapeutic indication who are still candidates for treatment with budesonide because they have not yet received budesonide. The G-BA specified budesonide as the ACT for this research question. In study parts A and B of the EE-1774 study, treatment with TCS, including budesonide, was not allowed within

8 weeks prior to baseline, as well as during the entire study duration. The use of TCS was only possible as rescue treatment. Furthermore, there is no exact information on how many patients in the EE-1774 study had already received budesonide in the past. In the dossier, the company only provided the number of patients with prior TCS therapy (74% in the placebo arm versus 69% in the dupilumab arm), but this number included both budesonide and fluticasone. In principle, however, regular treatment with budesonide was not planned in the EE-1774 study according to the study protocol, which is why this study – irrespective of the question of whether a subpopulation of the study can be delimited for research question 1 – is not suitable for answering this research question.

Research question 2 covers patients who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy. The ACT for this patient population as defined by the G-BA is BSC. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. In its notes on the ACT, the G-BA pointed out that PPIs may be indicated for the symptomatic treatment of heartburn or reflux symptoms.

In addition to the above-mentioned restrictions of the background treatment with TCS, treatment with PPIs was also restricted in study EE-1774. Patients receiving high-dose PPI therapy during the screening phase had to continue treatment for the entire study duration without dose adjustment. All other patients were not allowed to start treatment with PPIs during the study. As a result, about 31% of the included patients did not have access to PPIs for symptom relief. The remaining patients (69%) received high-dose PPI therapy during screening, which they had to continue for the entire period of the study. A dose reduction was not allowed. However, high-dose PPI therapy is not a symptomatic treatment in the sense of the ACT. According to the SPCs [6-9], PPIs for the symptomatic treatment of reflux symptoms should be used in lower doses and for a shorter treatment period than was the case in the study. Thus, according to the study protocol, no adequate symptomatic treatment with PPIs was possible for the patients in the EE-1774 study.

Furthermore, the S2k guideline recommends high-dose PPI therapy for the treatment of EoE, but treatment should be reassessed after 8 to 12 weeks and changed in case of non-response (= no clinical-histological remission) [1]. One inclusion criterion of study EE-1774 was non-response to at least 8 weeks of high-dose PPI therapy. Therefore, according to the S2k guideline, it does not seem reasonable to continue to expose patients without response to high-dose PPI therapy for the entire duration of the study.

In summary, since there were no options for need-based treatment adjustment, high-dose PPI therapy was continued despite the absence of clinical-histological remission, and standard PPI therapy for symptom control was not allowed in patients without high-dose PPI therapy. Hence, the ACT BSC was not implemented in the presented study parts A and B of study

EE-1774. Thus, no suitable data are available to answer research question 2, irrespective of the question of whether a subpopulation can be delimited for research question 2.

Conclusion

Study parts A and B of study EE-1774 are not suitable for answering the 2 research questions of the present benefit assessment because, irrespective of the lack of classification of the study population into the respective research questions, the corresponding ACTs were not implemented.

I 4 Results on added benefit

No suitable data are available for the assessment of the added benefit of dupilumab compared with the ACT in adults and adolescents 12 years and older, weighing at least 40 kg, with EoE, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy. There is no hint of added benefit of dupilumab in comparison with the ACT for either research question of the present benefit assessment; an added benefit is therefore not proven for either of them.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of dupilumab in comparison with the ACT is summarized in Table 5.

Table 5: Dupilumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with EoE who are still candidates for treatment with budesonide because they have not yet received budesonide[b]	Budesonide	Added benefit not proven
2	Adults and adolescents with EoE, 12 years and older, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy[c]	BSC[d, e]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. Adults who have not received prior treatment with budesonide and who are also not candidates for treatment with budesonide fall under research question 2.
c. According to the S2k guideline, conventional medicinal therapy includes topical corticosteroids and proton pump inhibitors [1].
d. BSC refers to the therapy which provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. Symptomatic treatment of heartburn or reflux symptoms with proton pump inhibitors may be indicated in the present therapeutic indication. Endoscopic dilatation treatment is assumed to be used sporadically in refractory cases and the presence of strictures. If elimination diets or avoidance diets achieved symptom reduction, e.g. in the context of allergic reactions to certain foods, it is assumed that these diets are continued.
e. In the present case, the drugs recommended in guidelines or used in clinical practice, that have no or no explicit approval for the present therapeutic indication, cannot be considered as ACT in the narrower sense within the meaning of §2 para 1 S. 3, §12 SGB V (BSG judgment of 22 February 2023, reference number: B 3 KR 14/21 R).

BSC: best supportive care; BSG: Federal Social Court; EoE: eosinophilic oesophagitis; G-BA: Federal Joint Committee; SGB: Social Code Book

The assessment described above deviates from that of the company, which derived proof of considerable added benefit for adults and adolescents 12 years and older with EoE.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a23-23.html.