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: COPD)

of 6 February 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 28 June 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 25 July 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 in adults as add-on maintenance treatment for uncontrolled chronic obstructive pulmonary disease (COPD) characterised by raised blood eosinophils on a

combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA), or on a combination of a LABA and a LAMA if ICS is not appropriate." 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 1 November 2024 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 resolution 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, as well of the addendum drawn up by the IQWiG on the benefit assessment. 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 in adults as add-on maintenance treatment for uncontrolled chronic obstructive pulmonary disease (COPD) characterised by raised blood eosinophils on a combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA), or on a combination of a LABA and a LAMA if ICS is not appropriate.

Therapeutic indication of the resolution (resolution of 06.02.2025):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with uncontrolled COPD characterised by raised blood eosinophils on a combination of ICS, LABA, and LAMA, or on a combination of LABA and LAMA if ICS is not appropriate, with a post-BD-FEV_1 ≥ 50% of target

Appropriate comparator therapy:

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

- LABA and LAMA and ICS, if applicable

b) Adults with uncontrolled COPD characterised by raised blood eosinophils on a combination of ICS, LABA, and LAMA, or on a combination of LABA and LAMA if ICS is not appropriate, with a post-BD-FEV_1 < 50% of target

Appropriate comparator therapy:

- LABA and LAMA and ICS, if applicable and roflumilast, provided that the criteria necessary for the administration of roflumilast are met

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. Depending on the therapeutic indication, various active ingredients from different product classes are available for the treatment of COPD:

- Selective beta2-agonists: Fenoterol, formoterol, indacaterol, olodaterol, salbutamol, salmeterol, vilanterol
- Anticholinergics: Aclidinium bromide, glycopyrronium bromide, ipratropium bromide, tiotropium bromide, umeclidinium bromide
- Corticosteroids: Beclometasone, budesonide, fluticasone, methylprednisolone, prednisolone, prednisone, triamcinolone
- Xanthines: Aminophylline, theophylline
- Phosphodiesterase inhibitors: Roflumilast

Various combination preparations are available for different combinations of active ingredients of selective long-acting beta2-agonists (LABA), long-acting muscarinic antagonists (LAMA) and inhaled corticosteroids (ICS). In addition, not all individual active ingredients are available in a mono-preparation, but only in a fixed combination preparation. The marketing authorisations of the medicinal products must be observed.

on 2. For the present therapeutic indication, a non-medicinal treatment is not considered as an appropriate comparator therapy.

on 3. The following resolutions of the G-BA are available on an amendment of the Pharmaceuticals Directive: Annex XII – Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Annex XII - Benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V: Indacaterol/ glycopyrronium (resolution of 8 May 2014)
- Annex XII - Benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V and Annex IX - Definition of reference price groups beta2-adrenergic agonists, inhaled oral, group 1, in stage 2 in accordance with Section 35a paragraph 3 in conjunction with paragraph 4 sentence 1 SGB V: Olodaterol (resolution of 17 July 2014)
- Annex XII - Benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V: Umeclidinium/ vilanterol (resolution of 8 January 2015)

- Annex XII - Benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V: Aclidinium bromide/ formoterol (resolution of 16 July 2015)
- Annex XII - Benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V: Tiotropium/ olodaterol (resolution of 4 February 2016)
- Annex XII - Benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V: Aclidinium bromide (resolution of 7 April 2016)
- Annex XII - Benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V: Umeclidinium (resolution of 21 July 2016)
- Annex XII - Benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V: Fluticasone/ umeclidinium/ vilanterol (resolution of 16 August 2018)
- Annex XII - Benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V: Fluticasone/ umeclidinium/ vilanterol (resolution of 02 May 2019)

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

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

Based on the available evidence, the 2021 German National Disease Management Guideline (NVL) for COPD recommends roflumilast as the final escalation stage to triple therapy (LAMA/LABA/ICS) if there is still a need for action due to an increased risk of exacerbation. In the event of ICS contraindications, roflumilast is also an add-on option to a LAMA/LABA combination instead of ICS.
For patients treated with LABA+LAMA+ICS who still have exacerbations, the "Global Initiative for Chronic Obstructive Lung Disease (GOLD)" guideline from 2023 also recommends considering escalation with roflumilast as an option for patients with an $FEV_1 < 50\%$ and chronic bronchitis, especially if they have had been hospitalised for an exacerbation at least once in the last year.
The German Respiratory Society (DGP), supported by the German Society of General Practice/Family Medicine (DEGAM), also points out in its written contribution that the treatment standard for COPD patients, who are not sufficiently controlled despite triple or dual therapy (if inhaled corticosteroids are contraindicated), is the additional administration of roflumilast ("in patients who repeatedly exacerbate despite therapy, who are to be classified as having the "chronic bronchitis" phenotype and have an $FEV_1 < 50\%$"). For adults with uncontrolled COPD characterised by raised blood eosinophils on a combination of ICS, LABA, and LAMA, or on a combination of LABA and LAMA if ICS is not appropriate, with a post-BD-$FEV_1 \geq 50\%$ of target, therapy with LABA and LAMA and, if applicable, ICS is therefore determined to be the appropriate comparator therapy. For adults with uncontrolled COPD characterised by raised blood eosinophils on a combination of ICS, LABA, and LAMA, or on a combination of LABA and LAMA if ICS is not appropriate, with a post-BD-$FEV_1 < 50\%$ of target, a combination therapy of LABA and LAMA and, if applicable, ICS and roflumilast is determined to be the appropriate comparator therapy, provided that the necessary criteria for the use of roflumilast are met.

The unchanged continuation of an inadequate therapy of COPD, if the option of therapy escalation still exists, does not correspond to an appropriate comparator therapy. Patient group b also includes patients who are already receiving triple therapy of LAMA/LABA/ICS or dual therapy of LAMA/LABA if ICS is not appropriate, but who do not fulfil the criteria (according to the marketing authorisation) for the additional use of roflumilast. For this group of patients, it should be justified that therapy escalation in accordance with the determined appropriate comparator therapy is not an option. Roflumilast may only be used as a possible appropriate comparator therapy in patients who fully meet the criteria of the marketing authorisation. According to the product information, treatment with roflumilast is "indicated for long-term therapy in adult patients with severe COPD (FEV_1 after use of a bronchodilator less than 50% of the target) and chronic bronchitis as well as frequent exacerbations in the past, in addition to bronchodilator therapy" (product information for roflumilast ELPEN, February 2022).
Both patient groups also include patients who are already receiving triple therapy, or dual therapy if ICS is not appropriate, and who continue to have symptoms. For these patients, measures that particularly affect the symptom of frequent exacerbations, such as acetylcysteine administration and saline inhalations, must be implemented.

Change of the appropriate comparator therapy

The appropriate comparator therapy was originally determined as follows:

Adults with uncontrolled COPD characterised by raised blood eosinophils on a combination of ICS, LABA, and LAMA, or on a combination of LABA and LAMA if ICS is not appropriate

Appropriate comparator therapy for dupilumab as add-on maintenance treatment:

- LABA and LAMA and ICS, if applicable and roflumilast, provided that the criteria necessary for the administration of roflumilast are met

However, for the benefit assessment, the pharmaceutical company only submitted results from the sub-populations of the BOREAS and NOTUS studies, each of which included patients with a post-BD-FEV_1 ≥ 50% of target at the start of the study. The criteria for the use of roflumilast are not met for this sub-population. In the present resolution, the patient population covered by the approved therapeutic indication is therefore divided into two patient groups.

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:

a) Adults with uncontrolled COPD characterised by raised blood eosinophils on a combination of ICS, LABA, and LAMA, or on a combination of LABA and LAMA if ICS is not appropriate, with a post-BD-FEV_1 ≥ 50% of target

Appropriate comparator therapy:

- LABA and LAMA and ICS, if applicable

Extent and probability of the additional benefit of dupilumab as add-on maintenance treatment compared with LABA and LAMA and ICS, if applicable:

Indication of a minor additional benefit

Justification:

For the benefit assessment, the pharmaceutical company presented results from the BOREAS and NOTUS studies – two double-blind randomised controlled trials comparing dupilumab with placebo. The study enrolled 939 adult patients aged ≥ 40 to ≤ 80 years (BOREAS) and 935 adult patients aged ≥ 40 to ≤ 85 years (NOTUS) with moderate-to-severe COPD (ratio of forced expiratory volume in 1 second [FEV_1] to forced vital capacity [FVC] < 0.70; 30% < FEV_1 ≤ 70% of target, each post-bronchodilator (post-BD); Medical Research Council [MRC] dyspnoea scale grade ≥ 2) and with signs and symptoms of chronic bronchitis (chronic productive cough) for 3 months in the year prior to the start of the study. Patients had to have a high risk of exacerbation, defined as ≥ 2 moderate or ≥ 1 severe exacerbation(s) within 1 year before the start of the study. At least 1 exacerbation should have occurred during treatment with an ICS (if indicated), LAMA and LABA. In addition, the patients had to show a raised number of eosinophils, defined as ≥ 300 cells/µl in the blood, at least once during the screening phase.

The BOREAS study was conducted between May 2019 and May 2023 and the NOTUS study between July 2020 and May 2024 at around 300 study sites worldwide (including Europe and Germany).

For the BOREAS study, the results of the final analysis are considered for all endpoints in the benefit assessment. The results of the final analysis are not yet available for the NOTUS study. For the present benefit assessment, the results of the interim analysis (data cut-off from 29 September 2023) are used for all endpoints. At the time of the interim analysis, 76.5% of patients in the dupilumab arm and 80.1% in the placebo arm of the relevant sub-population had completed the 52-week treatment phase (including patients who had prematurely discontinued treatment).

In the BOREAS and NOTUS studies, almost all patients received triple therapy consisting of LABA + LAMA + ICS. According to the inclusion criteria, the use of phosphodiesterase-4 (PDE-4) inhibitors such as roflumilast was only permitted if they had already been used as stable treatment for > 6 months prior to screening. This concerned 11 patients (1.2%) in the BOREAS study and 7 patients (0.7%) in the NOTUS study. According to the product information, roflumilast is indicated for severe COPD with a post-BD-FEV_1 < 50% of the target. For the benefit assessment, the pharmaceutical company therefore only presented the results of the

sub-populations of the BOREAS and NOTUS studies, each of which included patients with a post-BD-FEV_1 ≥ 50% of target at the start of the study. The criteria for the use of roflumilast are not met for this sub-population.

Suitability of the study population

No data were available in the dossier for the sub-population to show whether further options for therapy escalation would have existed at the start of the study and during its course, or whether the respective medicines were administered in accordance with the product information. A dose adjustment of the maintenance treatment was only permitted in the studies after one severe or two moderate COPD exacerbations.

In their statement, the pharmaceutical company presented post-hoc analyses that evaluate the percentage of patients with a post-BD-FEV_1 < 50% of target at least 6 weeks after a moderate or severe exacerbation. According to the pharmaceutical company, this is intended to determine the percentage of patients in a first approximation who might have been eligible for treatment with roflumilast in the course of the study. Based on this evaluation, no relevant percentage of patients in the sub-population post-BD-FEV_1 ≥ 50% of the BOREAS and NOTUS studies had a post BD-FEV_1 < 50% as a result of an exacerbation.

With their statement and following the oral hearing, the pharmaceutical company also submitted additional dosage information for ICS, LABA and LAMA. According to information provided by the pharmaceutical company, the percentage of patients in the relevant sub-population who received on-label treatment of the concomitant medication was 82.6% across both studies. A review of individual active ingredients shows that some of them were incorrectly assessed as being compliant with marketing authorisation for COPD. Therefore, there remains uncertainty overall regarding the percentage of patients who have not received on-label concomitant therapy for COPD. The dosage information subsequently submitted also shows that different doses were administered for frequently used ICS active ingredients such as budesonide and fluticasone propionate. In the written statement procedure, the Drugs Commission of the German Medical Association (AkdÄ) pointed out that transparent documentation of the reasons for or against dose escalation in the NOTUS and BOREAS studies would have been desirable. It is also unclear whether the inhalation technique was tested or optimised in accordance with the guidelines in the studies. In addition, guidelines recommend reviewing the possibility of de-escalation under certain circumstances in the case of high-dose ICS therapy. In the written statement procedure, the AkdÄ and the scientific-medical societies point out that the available evidence does not justify an advantage of a higher ICS dosage (or LAMA, LABA dosage); accordingly, the guidelines do not recommend dose escalation of the existing LAMA, LABA or ICS therapy in the event of inadequate symptom control.

For patients in the relevant sub-population in the comparator arm of the studies, the possibility of therapy escalation according to the study protocol was restricted and the review of de-escalation of existing ICS therapy was not planned. However, based on the information in the guidelines and that provided by the clinical experts, it is assumed that therapy escalation in the sense of a dose increase of ICS is not regularly recommended or used in everyday clinical practice for the patients in the relevant sub-population of the BOREAS and NOTUS studies. According to guideline recommendations, the review of de-escalation should only be considered if significant side effects (including pneumonia) occur.

Taking into account the statements of the clinical experts and the information in the documents subsequently submitted by the pharmaceutical company, it is therefore assumed that the appropriate comparator therapy is most adequately implemented for this patient group.

Extent and probability of the additional benefit

Mortality

For the endpoint of overall mortality, the meta-analysis did not show any statistically significant difference between the treatment groups.

Morbidity

Exacerbations (adjudicated)

In the BOREAS and NOTUS studies, exacerbations were documented by the principal investigator and confirmed by an external adjudication committee and defined as follows: "An acute event of deterioration of respiratory symptoms beyond the normal daily variation, leading to a change in medication. This usually involves an acute change in one or more of the following cardinal symptoms: i) increase in cough (frequency and severity), ii) increase in sputum production by volume and/or change in sputum type and iii) increase in dyspnoea". According to the study protocol, exacerbations were divided into moderate exacerbations (exacerbations that required treatment with either systemic corticosteroids (intramuscular, intravenous or oral) and/or antibiotics) and severe exacerbations (exacerbations that required hospitalisation or monitoring for 24 hours in an intensive care unit or resulted in death).
In the resolution, the endpoint of moderate or severe exacerbations or severe exacerbations is presented as the annual exacerbation rate (52 weeks) and additionally presented as the number of patients with exacerbation. Both for the endpoint of moderate or severe exacerbations and for the endpoint of severe exacerbations, the meta-analysis showed a statistically significant difference to the advantage of dupilumab compared to placebo.

Exacerbations of chronic pulmonary disease tool (EXACT)

Exacerbations were also assessed in the BOREAS and NOTUS studies using the EXACT questionnaire. In a daily diary, the questionnaire uses 14 questions to assess respiratory symptoms relating to breathlessness, cough and sputum, chest symptoms (11 questions) as well as 3 questions to assess insomnia, fatigue/ weakness and psychological status (worried/ anxious about lung problems). The EXACT was designed with patient involvement to assess exacerbations, defined as an increase of 12 points in the EXACT total score compared to baseline over 2 days or 9 points over 3 days (scale range 0 to 100). The definition is based on observations that the variability in a medically treated exacerbation is 9 to 12 points[2]. However, it is not sufficiently certain to what extent the defined criteria are used to actually detect a noticeable deterioration. These scores are below the response threshold of 15% of the scale range. Moreover, the EXACT does not reflect an intensification of COPD therapy. Overall, there is insufficient information to show that the EXACT evaluation algorithm reflects exacerbations. The EXACT results are therefore not taken into account.

Respiratory symptoms (E-RS:COPD)

The EXACT's 11 questions on respiratory symptoms form a stand-alone instrument (E-RS:COPD) that measures changes in respiratory symptomatology. The E-RS is used in the present benefit assessment to measure respiratory symptoms (improvement [response threshold of 15% of the scale range] at week 52 compared to the start of the study). For the endpoint of respiratory symptomatology, measured using the total score of E-RS:COPD, there is heterogeneity between the results from the BOREAS and NOTUS studies (p = 0.049). Since

[2] Leidy NK, Murray LT, Jones P, Sethi S. Performance of the exacerbations of chronic pulmonary disease tool patient-reported outcome measure in three clinical trials of chronic obstructive pulmonary disease. Ann Am Thorac Soc 2014; 11(3): 316-325.

heterogeneous results are only available for this endpoint, the assumption of a fixed-effect model is retained overall and the result of the corresponding meta-analytic summary is also used to derive the additional benefit for the endpoint of respiratory symptomatology.

The meta-analysis (as well as the individual studies) showed no statistically significant difference between the treatment groups.

Health status

For the endpoint of health status, assessed by EQ-5D VAS, there was no statistically significant difference between the treatment groups in the NOTUS study. No data is available for the BOREAS study.

Quality of life

St. Georges Respiratory Questionnaire (SGRQ)

Health-related quality of life was assessed using the SGRQ. The SGRQ includes the domains of symptoms, activity and everyday stress. A reduction in the score means an improvement. For the endpoint, there is an effect modification for the blood eosinophils characteristic at baseline. In the group of patients with < 300 cells/µl at baseline, there was no statistically significant difference between the treatment groups. In the group of patients with ≥ 300 cells/µl at baseline, there was a statistically significant difference to the advantage of dupilumab. However, the effect modification for this subgroup characteristic is only evident in the present endpoint.

For the SGRQ endpoint, measured using the total SGRQ score, the meta-analysis showed a statistically significant difference to the advantage of dupilumab compared to placebo.

Side effects

SAEs

For the endpoint of SAEs, the meta-analysis did not show any statistically significant difference between the treatment groups.

Therapy discontinuation due to AEs

For the endpoint of therapy discontinuation due to AEs, the meta-analysis did not show any statistically significant difference between the treatment groups.

Specific adverse events

No data are available for the relevant sub-population for the endpoints of eye disorders (SOC, AEs) and pneumonia (PT, AEs). For the endpoint of cardiovascular events (MACE), the meta-analysis did not show any statistically significant difference between the treatment groups.

Overall assessment

For the benefit assessment of dupilumab as add-on maintenance treatment in adults with uncontrolled COPD characterised by raised blood eosinophils on a combination of ICS, LABA, and LAMA, or on a combination of LABA and LAMA if ICS is not appropriate, with a post-BD-FEV_1 ≥ 50% of target, results of the two RCTs BOREAS and NOTUS are available for the endpoint categories of mortality, morbidity, health-related quality of life and side effects in comparison with a therapy consisting of LABA and LAMA and, if applicable, ICS.

For the endpoint of overall mortality, the meta-analysis did not show any statistically significant difference between the treatment groups.

For the endpoint of moderate or severe exacerbations and for the endpoint of severe exacerbations, the meta-analysis showed a statistically significant advantage of dupilumab compared to placebo in each case. The course of COPD is characterised by a progressive deterioration in lung function and increasing impairment of the well-being, in particular caused by recurrent exacerbations. However, only a few severe exacerbations occurred overall (in the BOREAS study, in 2.1% and 4.3% and in the NOTUS study, in 1.8% and 4.7% of patients in the intervention and control arm respectively). As a result, the reduction in the number of patients with severe exacerbations only showed an absolute difference of 2.2% and 2.9% respectively. Since most of the exacerbations that occurred during the studies were moderate - and not severe - exacerbations, the advantage shown is considered to be a moderate improvement.

For the endpoint of respiratory symptoms, assessed using the E-RS:COPD, and for the endpoint of health status, assessed using the EQ-5D VAS, there were no statistically significant differences between the treatment groups in the meta-analysis (E-RS:COPD) or in the NOTUS study (health status).

In the quality of life category, the meta-analysis showed a statistically significant advantage of dupilumab compared to placebo for the SGRQ endpoint. A significant difference can only be seen at the individual study level in the BOREAS study; the absolute difference in the number of patients with an improvement in quality of life is 8.2%. The advantage is therefore rated as moderate.

There were no statistically significant differences between the treatment groups in the side effects category.

In the overall assessment, a minor additional benefit was therefore identified for dupilumab as an add-on maintenance treatment for the present sub-population of patients with a post-BD-FEV_1 ≥ 50% of target compared with a maintenance treatment consisting of LABA and LAMA and if applicable ICS.

Reliability of data (probability of additional benefit)

The present assessment is based on a meta-analysis of two randomised, double-blind, placebo-controlled phase III studies (BOREAS and NOTUS). The cross-endpoint risk of bias is rated as low for both studies. The risk of bias at endpoint level is assessed as low for the endpoints of overall mortality, exacerbations, health-related quality of life (SGRQ) and therapy discontinuation due to AEs for the BOREAS and NOTUS studies.

For the endpoint of health status (EQ-5D VAS) (only assessed in the NOTUS study during the study) and for the endpoint of respiratory symptoms (E-RS:COPD), the risk of bias is assessed as high due to a high percentage of patients who were categorised as non-responders due to missing values. For the endpoint of SAEs, the risk of bias is assessed as high, as an unknown percentage of patients with AEs up to 98 days after discontinuation of dupilumab are included in the present analyses of AEs . In addition, an unknown percentage of disease-related events (exacerbations that were also classified as SAEs) are included in the analyses for the endpoint of SAEs.

The high risk of bias for the endpoints mentioned leads to uncertainties in the reliability of data. There are also uncertainties regarding the percentage of patients who did not receive

on-label COPD concomitant therapy. Taking into account the existence of a meta-analysis of two RCTs, the reliability of data is however classified as an indication overall.

b) Adults with uncontrolled COPD characterised by raised blood eosinophils on a combination of ICS, LABA, and LAMA, or on a combination of LABA and LAMA if ICS is not appropriate, with a post-BD-FEV_1 < 50% of target

Appropriate comparator therapy:

- LABA and LAMA and ICS, if applicable and roflumilast, provided that the criteria necessary for the administration of roflumilast are met

Extent and probability of the additional benefit of dupilumab as add-on maintenance treatment compared to the appropriate comparator therapy:

An additional benefit is not proven.

Justification:

In the present benefit assessment, statements can only be made - based on the data presented - on those patients in the BOREAS and NOTUS studies who have a post-BD-FEV_1 ≥ 50% of target. No data in comparison to the appropriate comparator therapy are available for patients with a post-BD-FEV_1 < 50% of target. An additional benefit is therefore not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient dupilumab. The therapeutic indication assessed here is as follows: "Dupixent is indicated in adults as add-on maintenance treatment for uncontrolled chronic obstructive pulmonary disease (COPD) characterised by raised blood eosinophils on a combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA), or on a combination of a LABA and a LAMA if ICS is not appropriate." In the therapeutic indication to be considered, two patient groups were distinguished:

a) Adults with uncontrolled COPD characterised by raised blood eosinophils on a combination of ICS, LABA, and LAMA, or on a combination of LABA and LAMA if ICS is not appropriate, with a post-BD-FEV_1 ≥ 50% of target

b) Adults with uncontrolled COPD characterised by raised blood eosinophils on a combination of ICS, LABA, and LAMA, or on a combination of LABA and LAMA if ICS is not appropriate, with a post-BD-FEV_1 < 50% of target

Patient population a)

A therapy consisting of LABA and LAMA and if applicable ICS was determined as the appropriate comparator therapy. For the assessment of the additional benefit of dupilumab, the pharmaceutical company presented results from the two randomised, double-blind, placebo-controlled phase III BOREAS and NOTUS studies on the endpoint categories of

mortality, morbidity, health-related quality of life and side effects in comparison with a therapy consisting of LABA and LAMA and if applicable ICS.

For the endpoint of overall mortality, the meta-analysis did not show any statistically significant difference between the treatment groups.

For the endpoint of moderate or severe exacerbations and for the endpoint of severe exacerbations, the meta-analysis showed a statistically significant advantage of dupilumab compared to placebo in each case. However, only very few severe exacerbations occurred overall, with most of them being moderate exacerbations. In addition, the reduction in the number of patients with severe exacerbations only showed an absolute difference of 2.2% and 2.9% respectively. The advantage shown is therefore rated as a moderate improvement.

For the endpoint of respiratory symptoms, assessed using the E-RS:COPD, and for the endpoint of health status, assessed using the EQ-5D VAS, there were no statistically significant differences between the treatment groups in the meta-analysis (E-RS:COPD) or in the NOTUS study (health status). In the quality of life category, the meta-analysis showed a statistically significant advantage of dupilumab compared to placebo for the SGRQ endpoint. Taking into account the magnitude of the difference, the advantage is rated as moderate. There were no statistically significant differences between the treatment groups in the side effects category.

In the overall assessment, a minor additional benefit was identified for dupilumab as an add-on maintenance treatment compared with a maintenance treatment consisting of LABA and LAMA and if applicable ICS.

There is uncertainty concerning the endpoints of health status (EQ-5D VAS), respiratory symptoms (E-RS:COPD) and SAEs, due to a high percentage of missing values or an unknown percentage of values that were received after discontinuation of dupilumab or contain disease-related events, as well as the information on the percentage of patients who did not receive on-label COPD concomitant therapy. Taking into account the existence of a meta-analysis of two RCTs, the reliability of data is however classified as an indication overall.

Patient population b)

A therapy consisting of LABA and LAMA and if applicable ICS and roflumilast was determined as the appropriate comparator therapy, provided that the necessary criteria for the use of roflumilast are met. For patient population b), the pharmaceutical company did not submit any data to prove the additional benefit. Therefore, 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).

The resolution is based on the patient numbers specified by the pharmaceutical company in the written statement procedure. The patient number estimated by the pharmaceutical company is subject to uncertainty overall and tends to be underestimated. The reason for this is in particular an incorrect reference of the percentage value of 2.93% for those patients who have exacerbations despite treatment with ICS + LABA + LAMA or, if ICS is not appropriate, treatment with LABA + LAMA. In addition, the target population was restricted to patients with a severity grade ≥ 2, which does not result from the therapeutic indication of dupilumab.

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: 16 October 2024):

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 COPD.

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: 1 January 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.

Since the inhaled corticosteroids (ICS) and the long-acting beta2 agonists (LABA) are assigned to a reference price group, one representative of each product class is shown as an example when deriving the costs. A representative of the fixed-dose combinations and the long-acting muscarinic antagonists (LAMA) is also presented as an example.

Treatment period:

a) Adults with uncontrolled COPD characterised by raised blood eosinophils on a combination of ICS, LABA, and LAMA, or on a combination of LABA and LAMA if ICS is not appropriate, with a post-BD-FEV_1 ≥ 50% of target

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 14 days	26.1	1	26.1
Long-acting muscarinic antagonists (LAMA)				
Tiotropium	Continuously, 1 x daily	365.0	1	365.0
Long-acting beta2 agonists (LABA)				
Formoterol	Continuously, 1 x daily	365.0	1	365.0
Inhaled corticosteroids (ICS)				
Fluticasone	Continuously, 2 x daily	365.0	1	365.0
LAMA + LABA fixed combination				
Umeclidinium I Vilanterol	Continuously, 1 x daily	365.0	1	365.0
LAMA + LABA + ICS fixed combination				
Beclometasone I Formoterol I Glycopyrronium	Continuously, 2 x daily	365.0	1	365.0
Appropriate comparator therapy				
LABA and LAMA and ICS, if applicable				
Long-acting muscarinic antagonists (LAMA)				
Tiotropium	Continuously, 1 x daily	365.0	1	365.0
Long-acting beta2 agonists (LABA)				
Formoterol	Continuously, 1 x daily	365.0	1	365.0
Inhaled corticosteroids (ICS)				
Fluticasone	Continuously, 2 x daily	365.0	1	365.0
LAMA + LABA fixed combination				
Umeclidinium I Vilanterol	Continuously, 1 x daily	365.0	1	365.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
LAMA + LABA + ICS fixed combination				
Beclometasone I Formoterol I Glycopyrronium	Continuously, 2 x daily	365.0	1	365.0
Long-acting muscarinic antagonists (LAMA)				
Tiotropium	Continuously, 1 x daily	365.0	1	365.0
Long-acting beta2 agonists (LABA)				
Formoterol	Continuously, 1 x daily	365.0	1	365.0
Inhaled corticosteroids (ICS)				
Fluticasone	Continuously, 2 x daily	365.0	1	365.0
LAMA + LABA fixed combination				
Umeclidinium I Vilanterol	Continuously, 1 x daily	365.0	1	365.0
LAMA + LABA + ICS fixed combination				
Beclometasone I Formoterol I Glycopyrronium	Continuously, 2 x daily	365.0	1	365.0

b) Adults with uncontrolled COPD characterised by raised blood eosinophils on a combination of ICS, LABA, and LAMA, or on a combination of LABA and LAMA if ICS is not appropriate, with a post-BD-FEV_1 < 50% of target

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 14 days	26.1	1	26.1
Long-acting muscarinic antagonists (LAMA)				
Tiotropium	Continuously, 1 x daily	365.0	1	365.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Long-acting beta2 agonists (LABA)				
Formoterol	Continuously, 1 x daily	365.0	1	365.0
Inhaled corticosteroids (ICS)				
Fluticasone	Continuously, 2 x daily	365.0	1	365.0
LAMA + LABA fixed combination				
Umeclidinium I Vilanterol	Continuously, 1 x daily	365.0	1	365.0
LAMA + LABA + ICS fixed combination				
Beclometasone I Formoterol I Glycopyrronium	Continuously, 2 x daily	365.0	1	365.0
Appropriate comparator therapy				
LABA and LAMA and ICS, if applicable and roflumilast				
Long-acting muscarinic antagonists (LAMA)				
Tiotropium	Continuously, 1 x daily	365.0	1	365.0
Long-acting beta2 agonists (LABA)				
Formoterol	Continuously, 1 x daily	365.0	1	365.0
Inhaled corticosteroids (ICS)				
Fluticasone	Continuously, 2 x daily	365.0	1	365.0
LAMA + LABA fixed combination				
Umeclidinium I Vilanterol	Continuously, 1 x daily	365.0	1	365.0
LAMA + LABA + ICS fixed combination				
Beclometasone I Formoterol I Glycopyrronium	Continuously, 2 x daily	365.0	1	365.0
Roflumilast				
Roflumilast	Continuously, 1 x daily	365.0	1	365.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Long-acting muscarinic antagonists (LAMA)				
Tiotropium	Continuously, 1 x daily	365.0	1	365.0
Long-acting beta2 agonists (LABA)				
Formoterol	Continuously, 1 x daily	365.0	1	365.0
Inhaled corticosteroids (ICS)				
Fluticasone	Continuously, 2 x daily	365.0	1	365.0
LAMA + LABA fixed combination				
Umeclidinium I Vilanterol	Continuously, 1 x daily	365.0	1	365.0
LAMA + LABA + ICS fixed combination				
Beclometasone I Formoterol I Glycopyrronium	Continuously, 2 x daily	365.0	1	365.0

Consumption:

a) Adults with uncontrolled COPD characterised by raised blood eosinophils on a combination of ICS, LABA, and LAMA, or on a combination of LABA and LAMA if ICS is not appropriate, with a post-BD-FEV_1 ≥ 50% of target

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	26.1	26.1 x 300 mg
Long-acting muscarinic antagonists (LAMA)					
Tiotropium	2.5 µg	5 µg	2 x 2.5 µg	365.0	730 x 2.5 µg
Long-acting beta2 agonists (LABA)					
Formoterol	12 µg	24 µg	2 x 12 µg	365.0	730 x 12 µg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Inhaled corticosteroids (ICS)					
Fluticasone	500 µg	1000 µg	2 x 500 µg	365.0	730 x 500 µg
LAMA + LABA fixed combination					
Umeclidinium I Vilanterol	55 µg/ 22 µg	55 µg/ 22 µg	1 x 55 µg/ 22 µg	365.0	365 x 55 µg/ 22 µg
LAMA + LABA + ICS fixed combination					
Beclometasone I Formoterol I Glycopyrronium	88 µg/ 5 µg/ 9 µg	176 µg/ 10 µg/ 18 µg	2 x 88 µg/ 5 µg/ 9 µg	365.0	730 x 88 µg/ 5 µg/ 9 µg
Appropriate comparator therapy					
LABA and LAMA and ICS, if applicable					
Long-acting muscarinic antagonists (LAMA)					
Tiotropium	2.5 µg	5 µg	2 x 2.5 µg	365.0	730 x 2.5 µg
Long-acting beta2 agonists (LABA)					
Formoterol	12 µg	24 µg	2 x 12 µg	365.0	730 x 12 µg
Inhaled corticosteroids (ICS)					
Fluticasone	500 µg	1000 µg	2 x 500 µg	365.0	730 x 500 µg
LAMA + LABA fixed combination					
Umeclidinium I Vilanterol	55 µg/ 22 µg	55 µg/ 22 µg	1 x 55 µg/ 22 µg	365.0	365 x 55 µg/ 22 µg
LAMA + LABA + ICS fixed combination					
Beclometasone I Formoterol I Glycopyrronium	88 µg/ 5 µg/ 9 µg	176 µg/ 10 µg/ 18 µg	2 x 88 µg/ 5 µg/ 9 µg	365.0	730 x 88 µg/ 5 µg/ 9 µg
Long-acting muscarinic antagonists (LAMA)					
Tiotropium	2.5 µg	5 µg	2 x 2.5 µg	365.0	730 x 2.5 µg
Long-acting beta2 agonists (LABA)					
Formoterol	12 µg	24 µg	2 x 12 µg	365.0	730 x 12 µg
Inhaled corticosteroids (ICS)					
Fluticasone	500 µg	1000 µg	2 x 500 µg	365.0	730 x 500 µg
LAMA + LABA fixed combination					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Umeclidinium I Vilanterol	55 µg/ 22 µg	55 µg/ 22 µg	1 x 55 µg/ 22 µg	365.0	365 x 55 µg/ 22 µg
LAMA + LABA + ICS fixed combination					
Beclometasone I Formoterol I Glycopyrronium	88 µg/ 5 µg/ 9 µg	176 µg/ 10 µg/ 18 µg	2 x 88 µg/ 5 µg/ 9 µg	365.0	730 x 88 µg/ 5 µg/ 9 µg

b) Adults with uncontrolled COPD characterised by raised blood eosinophils on a combination of ICS, LABA, and LAMA, or on a combination of LABA and LAMA if ICS is not appropriate, with a post-BD-FEV_1 < 50% of target

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					
Dupilmuab	300 mg	300 mg	1 x 300 mg	26.1	26.1 x 300 mg
Long-acting muscarinic antagonists (LAMA)					
Tiotropium	2.5 µg	5 µg	2 x 2.5 µg	365.0	730 x 2.5 µg
Long-acting beta2 agonists (LABA)					
Formoterol	12 µg	24 µg	2 x 12 µg	365.0	730 x 12 µg
Inhaled corticosteroids (ICS)					
Fluticasone	500 µg	1000 µg	2 x 500 µg	365.0	730 x 500 µg
LAMA + LABA fixed combination					
Umeclidinium I Vilanterol	55 µg/ 22 µg	55 µg/ 22 µg	1 x 55 µg/ 22 µg	365.0	365 x 55 µg/ 22 µg
LAMA + LABA + ICS fixed combination					
Beclometasone I Formoterol I Glycopyrronium	88 µg/ 5 µg/ 9 µg	176 µg/ 10 µg/ 18 µg	2 x 88 µg/ 5 µg/ 9 µg	365.0	730 x 88 µg/ 5 µg/ 9 µg
Appropriate comparator therapy					
LABA and LAMA and ICS, if applicable and roflumilast					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Long-acting muscarinic antagonists (LAMA)					
Tiotropium	2.5 µg	5 µg	2 x 2.5 µg	365.0	730 x 2.5 µg
Long-acting beta2 agonists (LABA)					
Formoterol	12 µg	24 µg	2 x 12 µg	365.0	730 x 12 µg
Inhaled corticosteroids (ICS)					
Fluticasone	500 µg	1000 µg	2 x 500 µg	365.0	730 x 500 µg
LAMA + LABA fixed combination					
Umeclidinium I Vilanterol	55 µg/ 22 µg	55 µg/ 22 µg	1 x 55 µg/ 22 µg	365.0	365 x 55 µg/ 22 µg
LAMA + LABA + ICS fixed combination					
Beclometasone I Formoterol I Glycopyrronium	88 µg/ 5 µg/ 9 µg	176 µg/ 10 µg/ 18 µg	2 x 88 µg/ 5 µg/ 9 µg	365.0	730 x 88 µg/ 5 µg/ 9 µg
Roflumilast					
Roflumilast	500 µg	500 µg	1 x 500 µg	365.0	365 x 500 µg
Long-acting muscarinic antagonists (LAMA)					
Tiotropium	2.5 µg	5 µg	2 x 2.5 µg	365.0	730 x 2.5 µg
Long-acting beta2 agonists (LABA)					
Formoterol	12 µg	24 µg	2 x 12 µg	365.0	730 x 12 µg
Inhaled corticosteroids (ICS)					
Fluticasone	500 µg	1000 µg	2 x 500 µg	365.0	730 x 500 µg
LAMA + LABA fixed combination					
Umeclidinium I Vilanterol	55 µg/ 22 µg	55 µg/ 22 µg	1 x 55 µg/ 22 µg	365.0	365 x 55 µg/ 22 µg
LAMA + LABA + ICS fixed combination					
Beclometasone I Formoterol I Glycopyrronium	88 µg/ 5 µg/ 9 µg	176 µg/ 10 µg/ 18 µg	2 x 88 µg/ 5 µg/ 9 µg	365.0	730 x 88 µg/ 5 µg/ 9 µg

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:

a) Adults with uncontrolled COPD characterised by raised blood eosinophils on a combination of ICS, LABA, and LAMA, or on a combination of LABA and LAMA if ICS is not appropriate, with a post-BD-FEV_1 ≥ 50% of target

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	€ 3,908.39	€ 2.00	€ 219.92	€ 3,686.47
Long-acting muscarinic antagonists (LAMA)					
Tiotropium 2.5 µg	180 SD	€ 197.86	€ 2.00	€ 10.33	€ 185.53
Long-acting beta2 agonists (LABA)					
Formoterol 12 µg[3]	180 SD	€ 84.00	€ 2.00	€ 5.75	€ 76.25
Inhaled corticosteroids (ICS)					
Fluticasone 500 µg[3]	120 SD	€ 45.55	€ 2.00	€ 2.71	€ 40.84
LAMA + LABA fixed combination					
Umeclidinium 55µg I Vilanterol 22 µg	30 SD	€ 155.40	€ 2.00	€ 7.98	€ 145.42
LAMA + LABA + ICS fixed combination					
Beclometasone 88 µg I Formoterol 5 µg I Glycopyrronium 9 µg	360 SD	€ 268.52	€ 2.00	€ 14.24	€ 252.28
Appropriate comparator therapy					
LABA and LAMA and ICS, if applicable					
Long-acting muscarinic antagonists (LAMA)					
Tiotropium 2.5 µg	180 SD	€ 197.86	€ 2.00	€ 10.33	€ 185.53
Long-acting beta2 agonists (LABA)					
Formoterol 12 µg[3]	180 SD	€ 84.00	€ 2.00	€ 5.75	€ 76.25

[3] Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Inhaled corticosteroids (ICS)					
Fluticasone 500 µg[3]	120 SD	€ 45.55	€ 2.00	€ 2.71	€ 40.84
LAMA + LABA fixed combination					
Umeclidinium 55µg I Vilanterol 22 µg	30 SD	€ 155.40	€ 2.00	€ 7.98	€ 145.42
LAMA + LABA + ICS fixed combination					
Beclometasone 88 µg I Formoterol 5 µg I Glycopyrronium 9 µg	360 SD	€ 268.52	€ 2.00	€ 14.24	€ 252.28
Abbreviations: SD = single doses; FCT = film-coated tablets; SFI = solution for injection					

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b) Adults with uncontrolled COPD characterised by raised blood eosinophils on a combination of ICS, LABA, and LAMA, or on a combination of LABA and LAMA if ICS is not appropriate, with a post-BD-FEV_1 < 50% of target

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	€ 3,908.39	€ 2.00	€ 219.92	€ 3,686.47
Long-acting muscarinic antagonists (LAMA)					
Tiotropium 2.5 µg	180 SD	€ 197.86	€ 2.00	€ 10.33	€ 185.53
Long-acting beta2 agonists (LABA)					
Formoterol 12 µg[4]	180 SD	€ 84.00	€ 2.00	€ 5.75	€ 76.25
Inhaled corticosteroids (ICS)					
Fluticasone 500 µg[3]	120 SD	€ 45.55	€ 2.00	€ 2.71	€ 40.84
LAMA + LABA fixed combination					
Umeclidinium 55µg I Vilanterol 22 µg	30 SD	€ 155.40	€ 2.00	€ 7.98	€ 145.42
LAMA + LABA + ICS fixed combination					
Beclometasone 88 µg I Formoterol 5 µg I Glycopyrronium 9 µg	360 SD	€ 268.52	€ 2.00	€ 14.24	€ 252.28
Appropriate comparator therapy					

[4] Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
LABA and LAMA and ICS, if applicable and roflumilast					
Long-acting muscarinic antagonists (LAMA)					
Tiotropium 2.5 µg	180 SD	€ 197.86	€ 2.00	€ 10.33	€ 185.53
Long-acting beta2 agonists (LABA)					
Formoterol 12 µg[3]	180 SD	€ 84.00	€ 2.00	€ 5.75	€ 76.25
Inhaled corticosteroids (ICS)					
Fluticasone 500 µg[3]	120 SD	€ 45.55	€ 2.00	€ 2.71	€ 40.84
LAMA + LABA fixed combination					
Umeclidinium 55µg I Vilanterol 22 µg	30 SD	€ 155.40	€ 2.00	€ 7.98	€ 145.42
LAMA + LABA + ICS fixed combination					
Beclometasone 88 µg I Formoterol 5 µg I Glycopyrronium 9 µg	360 SD	€ 268.52	€ 2.00	€ 14.24	€ 252.28
Roflumilast					
Roflumilast 500 µg[3]	90 FCT	€ 128.26	€ 2.00	€ 9.25	€ 117.01
Abbreviations: SD = single doses; FCT = film-coated tablets; SFI = solution for injection					

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.

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:

a) Adults with uncontrolled COPD characterised by raised blood eosinophils on a combination of ICS, LABA, and LAMA, or on a combination of LABA and LAMA if ICS is not appropriate, with a post-BD-FEV_1 ≥ 50% of target

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® 300 mg solution for injection in a pre-filled syringe/ Dupixent® 300 mg solution for injection in a pre-filled pen; last revised: June 2024

b) Adults with uncontrolled COPD characterised by raised blood eosinophils on a combination of ICS, LABA, and LAMA, or on a combination of LABA and LAMA if ICS is not appropriate, with a post-BD-FEV_1 < 50% of target

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.
References:
Product information for dupilumab (Dupixent); Dupixent® 300 mg solution for injection in a pre-filled syringe/ Dupixent® 300 mg solution for injection in a pre-filled pen; last revised: June 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 its session on 23 January 2024, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 25 July 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 2 VerfO.

By letter dated 25 July 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 28 October 2024, and the written statement procedure was initiated with publication on the G-BA website on 1 November 2024. The deadline for submitting statements was 22 November 2024.

The oral hearing was held on 9 December 2024.

By letter dated 10 December 2024, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 10 January 2025.

On 18 December 2024, the IQWiG submitted a new version of IQWiG's dossier assessment to the G-BA. This version 1.1 dated 18 December 2024 replaces version 1.0 of the dossier assessment dated 28 October 2024. The assessment result was not affected by the changes in version 1.1 compared to version 1.0.

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 28 January 2025, and the proposed draft resolution was approved.

At its session on 6 February 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	23 January 2024	Determination of the appropriate comparator therapy
Working group Section 35a	4 December 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	9 December 2024	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	18 December 2024 15 January 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	28 January 2025	Concluding discussion of the draft resolution
Plenum	6 February 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 6 February 2025

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

Prof. Hecken