Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee 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

At its session on 6 February 2025, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. In Annex XII, the following information shall be added after No. 5 to the information on the benefit assessment of Dupilumab in accordance with the resolution of 5 October 2023:

Dupilumab

Resolution of: 6 February 2025
Entry into force on: 6 February 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 28 June 2024):

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 6 February 2025):

See new therapeutic indication according to marketing authorisation.

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

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

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.

Study results according to endpoints:[1]

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment
Morbidity	↑↑	Advantage for exacerbations
Health-related quality of life	↑↑	Advantage for disease-specific quality of life
Side effects	↔	No relevant difference for the benefit assessment
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n.a.: not assessable		

BOREAS and NOTUS studies: Dupilumab versus placebo

Study design: randomised, double-blind, two-armed

Relevant sub-population: Populations with post-BD-FEV_1 (post-bronchodilator-forced expiratory volume in 1 second) ≥ 50%

[1] Data from the dossier assessment of the IQWiG (A24-79) and from the addendum (A24-118), unless otherwise indicated.

Mortality

Endpoint	Dupilumab		Placebo		Dupilumab vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI] p value[a]
Overall mortality[b]					
BOREAS	242	4 (1.7)	230	2 (0.9)	1.90 [0.35; 10.32] 0.456
NOTUS	217	4 (1.8)	236	3 (1.3)	1.45 [0.33; 6.43] 0.624
Total[c]					1.64 [0.54; 4.97] 0.385

a. RR, 95% CI and p value from logistic regression model with treatment as covariate; for the IPD meta-analysis, the study also as covariate in each case
b. The results on overall mortality are based on the data on fatal AEs.
c. IPD meta-analysis

Morbidity

Endpoint	Dupilumab		placebo		Dupilumab vs placebo
	N	Annual exacerbation rate [95% CI][b]	N	Annual exacerbation rate [95% CI][b]	Rate ratio [95% CI] p value[b] Absolute difference (AD)[e]
Annual exacerbation rate (52 weeks) - moderate or severe exacerbations[c, d]					
BOREAS	241	0.54 [0.39; 0.73]	231	0.78 [0.59; 1.03]	0.69 [0.51; 0.93] 0.014 0.24
NOTUS[e]	217	0.82 [0.56; 1.21]	236	1.35 [0.91; 2.02]	0.61 [0.43; 0.85] 0.004 0.53
Total[f]					0.66 [0.53; 0.82] < 0.001
Annual exacerbation rate (52 weeks) - severe exacerbations[c, g]					
BOREAS	241	0.16 [0.09; 0.29]	231	0.17 [0.10; 0.30]	0.93 [0.57; 1.50] 0.754
NOTUS[e]	217	0.04 [0.01; 0.12]	236	0.12 [0.05; 0.32]	0.34 [0.12; 0.97] 0.045 0.08
Total[f]					0.44 [0.20; 0.99] 0.047
Endpoint	Dupilumab		placebo		Dupilumab vs placebo

	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI] p value
Exacerbations (*presented additionally*, 52 weeks) - moderate or severe exacerbations[c, d]					
BOREAS	241	80 (33.2)	231	91 (39.4)	0.84 [0.66; 1.07] 0.167[h]
NOTUS[e]	217	61 (28.1)	236	84 (35.6)	0.79 [0.60; 1.04] 0.094[h]
Total					0.82 [0.68; 0.98] 0.029[i]
Exacerbations (*presented additionally*, 52 weeks) - severe exacerbations[c, g]					
BOREAS	241	5 (2.1)	231	10 (4.3)	0.48 [0.17; 1.38] 0.180[h]
NOTUS[e]	217	4 (1.8)	236	11 (4.7)	0.40 [0.13; 1.22] 0.097[h]
Total					0.44 [0.20; 0.94] 0.035[i]

a. Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
b. Negative binomial regression model with treatment group, region, ICS dose at baseline, smoking status at the time of screening, disease severity at baseline and number of moderate or severe exacerbations within one year prior to enrolment in the study as covariates and log-transformed duration of observation as offset variable; for IPD meta-analysis, the study also as covariate; treatment effect determined using delta method
c. Exacerbations were assessed by an independent committee. Accordingly, an exacerbation was defined as follows: 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 in volume and/or change in type of sputum, and iii) increase in dyspnoea
d. Exacerbations that required treatment with either systemic corticosteroids (intramuscular, intravenous or oral) and/or antibiotics (moderate) or that required hospitalisation or monitoring for 24 hours in an intensive care unit or resulted in death (severe)
e. In the NOTUS study, not all patients had completed the 52-week treatment phase at the time of the interim analysis (20% of patients in both study arms in the total population, information on the sub-population is not available).
f. IPD meta-analysis
g. Exacerbations that required hospitalisation or monitoring for 24 hours in an intensive care unit or resulted in death
h. IQWiG calculation: RR, CI (asymptotic) and p value (unconditional exact test, CSZ method according to Martin Andrés & Silva Mato, 1994)
i. IQWiG calculation: Meta-analysis with fixed effect (Mantel and Haenszel method)

Endpoint	Dupilumab		placebo		Dupilumab vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI] p value[a]
Respiratory symptoms (E-RS:COPD, improvement at week 52[b]), total score					
BOREAS	241	44 (18.3)	231	26 (11.3)	1.53 [0.98; 2.38] 0.061
NOTUS[c]	166	28 (16.9)	189	32 (16.9)	1.03 [0.66; 1.61] 0.882
Total[d]					1.21 [0.89; 1.64] 0.215
Respiratory symptoms (E-RS:COPD, improvement at week 52[b]), breathlessness					
BOREAS	241	56 (23.2)	231	31 (13.4)	1.58 [1.06; 2.36]
NOTUS[c]	166	35 (21.1)	189	39 (20.6)	1.04 [0.69; 1.55]
Total[d]					1.29 [0.98; 1.68]
Respiratory symptoms (E-RS:COPD, improvement at week 52[b]), cough and sputum					
BOREAS	241	41 (17.0)	231	34 (14.7)	1.09 [0.72; 1.64]
NOTUS[c]	166	32 (19.3)	189	37 (19.6)	0.84 [0.56; 1.27]
Total[e]					0.95 [0.71; 1.27]
Respiratory symptoms (E-RS:COPD, improvement at week 52[b]), chest symptoms					
BOREAS	241	43 (17.8)	231	31 (13.4)	1.17 [0.77; 1.78]
NOTUS[c]	166	28 (16.9)	189	34 (18.0)	0.92 [0.59; 1.43]
Total[d]					0.99 [0.74; 1.34]
Health status (EQ-5D VAS, improvement at week 52[g])					
BOREAS	Endpoint only collected for randomisation				
NOTUS[c]	166	50 (30.1)	189	35 (18.5)	1.32 [0.90; 1.95] 0.155

a. RR, 95% CI and p value from logistic regression model with treatment, region, ICS dose at baseline, smoking status at the time of screening and the corresponding baseline values as covariates; for the IPD meta-analysis, the study also as a covariate in each case

b. A decrease in the score by ≥ 6 points (total score), ≥ 2.55 points (breathlessness), ≥ 1.65 (cough and sputum), ≥ 1.8 points (chest symptoms) compared to the start of the study is considered as clinically relevant improvement (total score range: 0 to 40, breathlessness: 0 to 17, cough and sputum: 0 to 11, chest symptoms: 0 to 12). Patients with missing values at week 52 were counted as non-responders.

c. Only patients who completed the 52-week treatment phase or would have completed it if they had not discontinued treatment beforehand were considered.

d. In the present data basis, despite statistically significant heterogeneity in the total score of E-RS:COPD (p = 0.049), as well as the subscales of breathlessness (p = 0.006) and chest symptoms (p = 0.046), the joint effect estimator is presented.

e. IPD meta-analysis

g. An increase in score by ≥ 15 points compared to the start of the study is considered as clinically relevant improvement (range of values of both scales: 0 to 100). Patients with missing values at week 52 were counted as non-responders.

Health-related quality of life

Endpoint	Dupilumab		placebo		Dupilumab vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI] p value[b] Absolute difference (AD)[a]
SGRQ (total score[c], improvement at week 52[d]					
BOREAS	241	77 (32.0)	231	55 (23.8)	1.36 [1.03; 1.80] 0.029 22
NOTUS[e]	166	52 (31.3)	189	42 (22.2)	1.30 [0.93; 1.80] 0.120
Total[f]					1.34 [1.09; 1.65] 0.005

a. Indication of absolute difference (AD) only in case of statistically significant difference; own calculation
b. RR, 95% CI and p value from logistic regression model with treatment, region, ICS dose at baseline, smoking status at the time of screening and the corresponding baseline values as covariates; for the IPD meta-analysis, the study also as covariate in each case
c. No suitable responder analyses are available for the subscales of symptoms, activity and psychosocial impact.
d. A decrease in score by ≥ 15 points compared to the start of study is considered as clinically relevant improvement (range of values of both scales: 0 to 100). Patients with missing values at week 52 were counted as non-responders.
e. Only patients who completed the 52-week treatment phase or would have completed it if they had not discontinued treatment beforehand were considered.
f. IPD meta-analysis

Side effects

Endpoint	Dupilumab		placebo		Dupilumab vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	Relative risk [95% CI] p value[a]
Total adverse events *(presented additionally)*[b]					
BOREAS	242	185 (76.4)	230	177 (77.0)	-
NOTUS	217	144 (66.4)	236	154 (65.3)	-
Serious adverse events (SAE)[c]					
BOREAS	242	22 (9.1)	230	26 (11.3)	0.80 [0.47; 1.38] 0.428
NOTUS	217	18 (8.3)	236	26 (11.0)	0.75 [0.42; 1.34] 0.331
Total[d]					0.78 [0.53; 1.15] 0.213

Therapy discontinuation due to adverse events					
BOREAS	242	8 (3.3)	230	7 (3.0)	1.09 [0.40; 2.95] 0.871
NOTUS	217	10 (4.6)	236	7 (3.0)	1.55 [0.60; 4.02] 0.363
Total[d]					1.31 [0.66; 2.61] 0.436
Specific adverse events					
Eye disorders (SOC, AEs)			No information on the relevant sub-population[e]		
Conjunctivitis (broad CMQ[f], AEs, presented additionally)			No information on the relevant sub-population[g]		
Pneumonia (PT, AEs)			No information on the relevant sub-population[h]		
Cardiovascular events (MACE[i])					
BOREAS	242	3 (1.2)	230	5 (2.2)	0.57 [0.14; 2.37] 0.439
NOTUS	217	1 (0.5)	236	3 (1.3)	0.36 [0.04; 3.48] 0.378
Total[d]					0.50 [0.15; 1.64] 0.251

a. RR, 95% CI and p value from logistic regression model with treatment as covariate; for the IPD meta-analysis, the study also as covariate in each case
b. Analysis excluding the disease-specific PTs "COPD", "Chronic bronchitis" and excluding exacerbations (with the exception of exacerbations that were simultaneously categorised as SAEs)
c. Analysis excluding the disease-specific PTs "COPD", "Chronic bronchitis"; exacerbations that were simultaneously classified as SAEs were not excluded.
d. IPD meta-analysis
e. < 10 patients in both study arms; in the total population, 8 (1.7%) vs 9 (1.9%) patients in the BOREAS study and 10 (2.1%) vs 5 (1.1%) patients in the NOTUS study had at least 1 event.
f. Pre-specified operationalisation for conjunctivitis with 16 PTs
g. < 10 patients in both study arms; In the total population, 5 (1.1%) vs 9 (1.9%) patients in the BOREAS study and 10 (2.1%) vs 4 (0.9%) patients in the NOTUS study had at least 1 event.
h. < 10 patients in both study arms; in the total population, 13 (2.8%) vs 19 (4.0%) patients in the BOREAS study and 8 (1.7%) vs 6 (1.3%) patients in the NOTUS study had at least 1 event.
i. Assessed; includes cardiovascular death, non-fatal myocardial infarction and non-fatal stroke; no data available for the individual components.

Abbreviations used:
AD = absolute difference: CMQ: Customised MedDRA Query; COPD: chronic obstructive pulmonary disease; CRF: Case Report Form; E-RS:COPD: Evaluating Respiratory Symptoms in COPD; FEV1: forced expiratory volume in 1 second; ICS: inhaled corticosteroid; IPD: individual patient data; CI: confidence interval; MACE: Major Adverse Cardiovascular Event; n: number of patients with (at least 1) event; N: number of patients evaluated; Post-BD-FEV1: post-bronchodilator-forced expiratory volume in 1 second; PT: preferred term; RCT: randomised controlled trial; SGRQ: St George's Respiratory Questionnaire; SOC: system organ class; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale

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 data available.

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	No data available.
Morbidity	∅	No data available.
Health-related quality of life	∅	No data available.
Side effects	∅	No data available.

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: No data available.
n.a.: not assessable

2. Number of patients or demarcation of patient groups eligible for treatment

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

Approx. 6,650 patients

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

Approx. 2,720 patients

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.

4. Treatment costs

Annual treatment costs:

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	Annual treatment costs/ patient
Medicinal product to be assessed:	
Dupilumab	€ 16,036.14
Long-acting muscarinic antagonists (LAMA)	
Tiotropium	€ 752.43
Long-acting beta2 agonists (LABA)	
Formoterol**Fehler! Textmarke nicht definiert.**	€ 309.24
Inhaled corticosteroids (ICS)	
Fluticasone**Fehler! Textmarke nicht definiert.**	€ 248.44
LAMA + LABA fixed combination	
Umeclidinium I Vilanterol	€ 589.76
LAMA + LABA + ICS fixed combination	
Beclometasone I Formoterol I Glycopyrronium	€ 511.57
Appropriate comparator therapy:	
LABA and LAMA and ICS, if applicable	
Long-acting muscarinic antagonists (LAMA)	
Tiotropium	€ 752.43
Long-acting beta2 agonists (LABA)	
Formoterol**Fehler! Textmarke nicht definiert.**	€ 309.24
Inhaled corticosteroids (ICS)	
Fluticasone**Fehler! Textmarke nicht definiert.**	€ 248.44
LAMA + LABA fixed combination	
Umeclidinium I Vilanterol	€ 589.76
LAMA + LABA + ICS fixed combination	
Beclometasone I Formoterol I Glycopyrronium	€ 511.57
Long-acting muscarinic antagonists (LAMA)	

Designation of the therapy	Annual treatment costs/ patient
Tiotropium	€ 752.43
Long-acting beta2 agonists (LABA)	
Formoterol[Fehler! Textmarke nicht definiert.]	€ 309.24
Inhaled corticosteroids (ICS)	
Fluticasone[Fehler! Textmarke nicht definiert.]	€ 248.44
LAMA + LABA fixed combination	
Umeclidinium I Vilanterol	€ 589.76
LAMA + LABA + ICS fixed combination	
Beclometasone I Formoterol I Glycopyrronium	€ 511.57

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	Annual treatment costs/ patient
Medicinal product to be assessed:	
Dupilumab	€ 16,036.14
Long-acting muscarinic antagonists (LAMA)	
Tiotropium	€ 752.43
Long-acting beta2 agonists (LABA)	
Formoterol[Fehler! Textmarke nicht definiert.]	€ 309.24
Inhaled corticosteroids (ICS)	
Fluticasone[Fehler! Textmarke nicht definiert.]	€ 248.44
LAMA + LABA fixed combination	
Umeclidinium I Vilanterol	€ 589.76
LAMA + LABA + ICS fixed combination	
Beclometasone I Formoterol I Glycopyrronium	€ 511.57
Appropriate comparator therapy:	
LABA and LAMA and ICS, if applicable and roflumilast	
Long-acting muscarinic antagonists (LAMA)	
Tiotropium	€ 752.43
Long-acting beta2 agonists (LABA)	

Designation of the therapy	Annual treatment costs/ patient
Formoterol[Fehler! Textmarke nicht definiert.]	€ 309.24
Inhaled corticosteroids (ICS)	
Fluticasone[Fehler! Textmarke nicht definiert.]	€ 248.44
LAMA + LABA fixed combination	
Umeclidinium I Vilanterol	€ 589.76
LAMA + LABA + ICS fixed combination	
Beclometasone I Formoterol I Glycopyrronium	€ 511.57
Roflumilast	
Roflumilast[2]	€ 474.54
Long-acting muscarinic antagonists (LAMA)	
Tiotropium	€ 752.43
Long-acting beta2 agonists (LABA)	
Formoterol[Fehler! Textmarke nicht definiert.]	€ 309.24
Inhaled corticosteroids (ICS)	
Fluticasone[Fehler! Textmarke nicht definiert.]	€ 248.44
LAMA + LABA fixed combination	
Umeclidinium I Vilanterol	€ 589.76
LAMA + LABA + ICS fixed combination	
Beclometasone I Formoterol I Glycopyrronium	€ 511.57

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 January 2025

Costs for additionally required SHI services: not applicable

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

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

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

[2] Fixed reimbursement rate

– 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.

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.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. 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.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 6 February 2025.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 6 February 2025

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

Prof. Hecken