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: atopic dermatitis, 6 months to 5 years)

of 21 September 2023

At its session on 21 September 2023, 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 21 September 2023 on therapeutic indication "Treatment of eosinophilic oesophagitis, ≥ 12 years, min. 40 kg":**

Dupilumab

Resolution of: 21 September 2023
Entry into force on: 21 September 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 15 March 2023):

Treatment of severe atopic dermatitis in children 6 months to 5 years of age who are candidates for systemic therapy**.**

Therapeutic indication of the resolution (resolution of 21 September 2023):

See new therapeutic indication according to marketing authorisation.

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

a) Children from 6 months to 5 years of age with severe atopic dermatitis who are candidates for systemic therapy and whose clinical picture is sufficiently similar to that of adults

Appropriate comparator therapy:

A patient-individual optimized therapy regime depending on the manifestation of the disease and taking into account the previous therapy, selecting the following therapies:

- topical glucocorticoids of classes 1 to 3
- Tacrolimus (topical)

Extent and probability of the additional benefit of dupilumab compared to the appropriate comparator therapy:

Hint for a non-quantifiable additional benefit.

b) Children from 6 months to 5 years of age with severe atopic dermatitis who are candidates for systemic therapy and whose clinical picture is not sufficiently similar to that of adults

Appropriate comparator therapy:

A patient-individual optimized therapy regime depending on the manifestation of the disease and taking into account the previous therapy, selecting the following therapies:

- topical glucocorticoids of classes 1 to 3
- Tacrolimus (topical)

Extent and probability of the additional benefit of dupilumab compared to the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:[1]

a) Children from 6 months to 5 years of age with severe atopic dermatitis who are candidates for systemic therapy and whose clinical picture is sufficiently similar to that of adults

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↑	Advantages for symptoms of itching and sleep disturbance, patient-reported symptomatology, and improvement in EASI score by 75% and 90%, and improvement in SCORAD score by 75%.
Health-related quality of life	↑	Advantage in achieving a DLQI of 0 or 1.
Side effects	↓	Disadvantage in eye disorders, but not evident in the PRESCHOOL study presented additionally.
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 ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

Transfer of the results of the age stratum ≥ 18 to < 40 years of the CHRONOS study to children from 6 months to 5 years of age whose clinical picture is sufficiently similar to that of adults:

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A23-25) unless otherwise indicated.

Morbidity

Study endpoint category Endpoint	Dupilumab + TCS		Placebo + TCS		Dupilumab + TCS vs Placebo + TCS
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
CHRONOS (week 52)[a] - age stratum ≥ 18 to < 40 years					
Symptomatology					
Itching – peak pruritus NRS (improvement of ≥ 4 points)[b]	50	31 (62.0)	182	59 (32.4)	1.86 [1.37; 2.53]; < 0.001[c]
Response (EASI 75)	52	35 (67.3)	189	89 (47.1)	1.37 [1.07; 1.76]; 0.014[c]
Response (EASI 90)	52	26 (50.0)	189	54 (28.6)	1.58 [1.12; 2.24]; 0.010[c]
Response (SCORAD 75)	52	19 (36.5)	189	33 (17.6)	1.85 [1.16; 2.96]; 0.010[c]
Response (SCORAD 90)	52	7 (13.5)	189	14 (7.4)	1.56 [0.68; 3.59]; 0.291[c]

Study endpoint category Endpoint	Dupilumab + TCS			Placebo + TCS			Dupilumab + TCS vs Placebo + TCS
	N[d]	Values at the start of the study MV (SD)	Change during week 52 MV[e] (SE)	N[d]	Values at the start of the study MV (SD)	Change during week 52 MV[e] (SE)	MD [95% CI]; p value[e]
CHRONOS (week 52)[a] - age stratum ≥ 18 to < 40 years							
Symptomatology							
Patient-reported symptomatology – POEM[f]	52	20.5 (5.15)	-12.5 (0.94)	189	20.4 (6.00)	-7.1 (0.52)	-5.5 [-7.54; -3.41]; < 0.001 Hedges' g: -0.85 [-1.16; -0.53]
Sleep disorders - SCORAD VAS[f]	52	5.4 (3.31)	-4.1 (0.27)	189	4.9 (3.22)	-2.9 (0.14)	-1.2 [-1.75; -0.59]; < 0.001 Hedges' g: -0.65 [-0.97; -0.33]
Health status							
EQ-5D VAS[g]	52	58.4 (22.10)	20.1 (2.26)	189	55.2 (22.87)	15.4 (1.25)	4.7 [-0.28; 9.64]; 0.064

Health-related quality of life

Study endpoint category Endpoint	Dupilumab + TCS		Placebo + TCS		Dupilumab + TCS vs Placebo + TCS
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
CHRONOS (week 52)[a] - age stratum ≥ 18 to < 40 years					
Health-related quality of life					
DLQI (0 or 1)	52	23 (44.2)	189	30 (15.9)	2.64 [1.69; 4.12]; < 0.001[c]

Side effects

Study endpoint category Endpoint	Dupilumab + TCS		Placebo + TCS		Dupilumab + TCS vs Placebo + TCS
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
CHRONOS (week 52)[a] - age stratum ≥ 18 to < 40 years					
Side effects					
Eye disorders (SOC, AEs)	55	17 (30.9)	189	22 (11.6)	2.66 [1.52; 4.65]; < 0.001
supplementary: Conjunctivitis (broad CMQ)[h]	110	27 (24.5)	315	35 (11.1)	2.21 [1.40; 3.47]; < 0.001[i]

[a] In part, numerically deviating values result from the data of the present dossier compared to A17-63 (total population) or A20-01 (stratum ≥ 18 to < 40 years), which, however, do not lead to a qualitatively deviating statement. Unless otherwise stated, the values reported in Module 4 I of the dossier are presented.
[b] Percentage of patients with a decrease of ≥ 4 points compared to the start of the study at week 52 with a scale range of 0 to 10. Lower values mean an improvement of symptomatology.
[c] Logistic regression model, adjusted for variables of randomisation stratification
[d] Number of patients who were taken into account in the evaluation for calculating the effect estimate; the values at start of study can be based on other patient numbers.
[e] MI evaluation of the ITT population. Analysis of covariance (ANCOVA) with corresponding baseline values, treatment arm and randomisation stratification variables (region and severity of disease [IGA 3 vs IGA 4] at baseline) as covariates. All observed values are included in the analysis, missing values are filled in by MI in two stages (MCMC and regression analysis).
[f] Lower (decreasing) values mean better symptomatology; negative effects (intervention minus control) mean an advantage for the intervention (scale range 0 to 28 [POEM] or 0 to 10 [SCORAD VAS]).
[g] Higher (increasing) values mean better health status; positive effects (intervention minus control) mean an advantage for the intervention (scale range 0 to 100).
[h] Post hoc operationalisation on conjunctivitis with 16 PTs (conjunctivitis broad CMQ). The study on conjunctivitis events is based on the increased incidence of conjunctivitis and other eye disorders selected during therapy with dupilumab. The data come from the dossier assessment A17-63.
[i] IQWiG calculation: 95% CI asymptotic, unconditional exact test (CSZ method)

Abbreviations used: ANCOVA: Analysis of covariance; CMQ: Customized MedDRA Query; DLQI: Dermatology Life Quality Index; FDA: U. S. Food and Drug Administration; EQ-5D: European Quality of Life Questionnaire

– 5 Dimensions; CI: confidence interval; MCMC: Markov Chain Monte Carlo; MD: Mean difference; MedDRA: Medical Dictionary for Regulatory Activities; MI: multiple imputation; MV: mean value; n: number of patients with (at least 1) event; N: number of patients evaluated; NRS: Numerical Rating Scale; POEM: Patient-Oriented Eczema Measure; PT: preferred term; RCT: randomised controlled trial; RR: relative risk; SCORAD: Scoring Atopic Dermatitis; SD: standard deviation; SE: standard error; SOC: system organ class; TCS: topical glucocorticoids

PRESCHOOL study results presented additionally:

Morbidity

Study endpoint category Endpoint	**Dupilumab + TCS**		**Placebo + TCS**		Dupilumab + TCS vs Placebo + TCS
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[j]
PRESCHOOL (week 16)					
Symptomatology					
Itching - worst scratch/ itch score (improvement by ≥ 4 points)[k]	83	44 (53.0)	79	11 (14.1)	3.82 [2.13; 6.85]; < 0.001
Response (EASI 75)	83	53 (63.9)	79	13 (16.5)	3.44 [2.03; 5.85]; < 0.001
Response (EASI 90)	83	23 (27.7)	79	2 (2.5)	7.45 [1.80; 30.77]; 0.006
Response (SCORAD 75)	83	22 (26.5)	79	1 (1.3)	21.02 [2.91; 151.99]; 0.003
Response (SCORAD 90)	83	3 (3.6)	79	0 (0)	6.67 [0.35; 127.0]; 0.207[l]

Study endpoint category Endpoint	Dupilumab + TCS			Placebo + TCS			Dupilumab + TCS vs Placebo + TCS
	N[m]	Values at the start of the study MV (SD)	Change during week 52 MV[n] (SE)	N[m]	Values at the start of the study MV (SD)	Change during week 52 MV[n] (SE)	MD [95% CI]; p value[n]
PRESCHOOL (week 16)							
Symptomatology							
Patient-reported symptomatology – POEM[o]	83	23.1 (4.49)	-13.32 (0.85)	79	23.29 (4.04)	-5.95 (0.89)	-7.37 [-9.59; -5.16]; < 0.001 SMD: -1.03 [-1.34; -0.72]
Sleep disorders - SCORAD VAS[o]	83	7.14 (2.32)	-4.77 (0.34)	79	7.02 (2.11)	-2.49 (0.36)	-2.29 [-3.19; -1.39], < 0.001 SMD: -0.79 [-1.10; -0.48]
Health status							
EQ-5D VAS					-[p]		

Health-related quality of life

Study endpoint category Endpoint	Dupilumab + TCS		Placebo + TCS		Dupilumab + TCS vs Placebo + TCS
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[j]
PRESCHOOL (week 16)					
Health-related quality of life					
CDLQI (0 or 1)[q]	47	4 (8.5)	38	2 (5.3)	1.20 [0.22; 6.46]; 0.832
IDQOL (0 or 1)[q]	36	7 (19.4)	41	1 (2.4)	7.98 [1.02; 62.36], 0.048

Side effects

Study endpoint category Endpoint	Dupilumab + TCS		Placebo + TCS		Dupilumab + TCS vs Placebo + TCS
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[j]
PRESCHOOL (week 16)					
Side effects					
Eye disorders (SOC, AEs)	83	3 (3.6)	78	3 (3.8)	0.94 [0.20; 4.52], 0.999[r]
supplementary: Conjunctivitis or blepharitis (broad CMQ)[s]	83	6 (7.2)	78	1 (1.3)	5.64 [0.68; 46.53], 0.108

[j] LOCF evaluation of the safety population as randomised (ITT). RR: according to the pharmaceutical company, derived from the Mantel-Haenszel estimator, the p value of the RR is calculated from the effect estimate and the confidence interval of the RR. All collected data are considered for the evaluation. This also applies to data collected after a study was discontinued or after the use of medication or rescue therapy prohibited by the study design.

[k] Percentage of patients with a decrease of ≥ 4 points compared to the start of the study at week 16 with a scale range of 0 to 10. The itching was recorded as a third-party assessment by parents/ guardians.

[l] According to the pharmaceutical company, an unadjusted RR with zero cell correction was calculated, the value 0.5 was added to each cell of the four-field table; the CI was calculated under normal distribution approximation.

[m] Number of patients included in the evaluation for the calculation of the effect estimate.

[n] MI evaluation of the ITT population. Estimation according to the least squares method in an analysis of covariance (ANCOVA) with the respective baseline values, treatment arm and randomisation stratification variables (weight, disease severity [IGA 3 vs IGA 4] and region at baseline) as covariates. All observed values are included in the analysis, missing values are filled in by MI in two stages (MCMC and regression analysis).

[o] Lower values mean better symptomatology; negative effects (intervention minus control) mean an advantage for the intervention (scale range 0 to 28 [POEM] or 0 to 10 [SCORAD VAS]). The POEM was recorded as a third-party assessment by parents/ guardians, the SCORAD-VAS was recorded by the patient or as a third-party assessment by parents/ guardians.

[p] Endpoint not assessed

[q] In the PRESCHOOL study, instead of the DLQI, the CDLQI was used for children aged 4 years and older and the IDQOL (IDQOL was recorded as a third-party assessment by parents/ guardians) for children under 4 years. The questionnaires are valid tools for assessing health-related quality of life in the respective age group. Only patients with almost any limitations or none in health-related quality of life (DLQI or CDLQI or IDQOL = 0 or 1) are shown.

[r] RR and CI: IQWiG calculation; p value: IQWiG calculation, unconditional exact test (CSZ method);

[s] Pre-specified operationalisation for conjunctivitis with 16 PTs (broad conjunctivitis CMQ).

Abbreviations used: ANCOVA: Analysis of covariance; CMQ: Customized MedDRA Query; DLQI: Dermatology Life Quality Index; EQ-5D: European Quality of Life Questionnaire - 5 Dimensions; FAS: Full Analysis Set; FDA: U. S. Food and Drug Administration; n. A.: no data; CI: confidence interval; MD: Mean difference; MedDRA: Medical Dictionary for Regulatory Activities; mFAS: modified full analysis set; MV: mean value; n: number of patients with (at least 1) event; N: number of patients evaluated; NRS: Numerical Rating Scale; POEM: Patient-Oriented Eczema Measure;; PT: preferred term; Q4W: once every 4 weeks; RCT: randomised controlled trial; RR: relative risk; SCORAD: Scoring Atopic Dermatitis; SD: standard deviation; SE: standard error; SOC: system organ class; TCS: topical glucocorticoids; VAS: visual analogue scale

b) Children from 6 months to 5 years of age with severe atopic dermatitis who are candidates for systemic therapy and whose clinical picture is not sufficiently similar to that of adults

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	There are no assessable data.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	n.a.	There are no assessable data.
Side effects	n.a.	There are no assessable data.
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		

No suitable data submitted.

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

Children 6 months to 5 years of age with severe atopic dermatitis who are candidates for systemic therapy

Approx. 2,700 to 3,900 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: 30 May 2023):

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

4. Treatment costs

Annual treatment costs:

Children 6 months to 5 years of age with severe atopic dermatitis who are candidates for systemic therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Dupilumab	€ 7,807.80
Appropriate comparator therapy:	
Prednisolone[2]	Different from patient to patient
Hydrocortisone butyrate[3]	Different from patient to patient
Methylprednisolone[4]	Different from patient to patient
Tacrolimus	Different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 September 2023

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) Children from 6 months to 5 years of age with severe atopic dermatitis who are eligible for systemic therapy and whose clinical picture is sufficiently similar to that of adults

- 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.

b) Children from 6 months to 5 years of age with severe atopic dermatitis who are eligible for systemic therapy and whose clinical picture is not sufficiently similar to that of adults

- 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.

[2] Prednisolone is presented as an example for class I topical glucocorticoids.
[3] Hydrocortisone butyrate is exemplified for the topical glucocorticoids of class II.
[4] Methylprednisolone is exemplified for the topical glucocorticoids of class III.

II. **The resolution will enter into force on the day of its publication on the website of the G-BA on 21 September 2023.**

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

Berlin, 21 September 2023

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

Prof. Hecken