Gemeinsamer Bundesausschuss

Dupilumab (New Therapeutic Indication: Atopic dermatitis, 6 to 11 years of age)

Resolution of: 1 July 2021 Valid until: unlimited
Entry into force on: 1 July 2021
BAnz AT 22 07 2021 B2

New therapeutic indication (according to the marketing authorisation of 25 November 2020):

Dupixent is indicated for the treatment of severe atopic dermatitis in children 6 to 11 years old who are candidates for systemic therapy.

Therapeutic indication of the resolution (resolution of 1 July 2021):

see new therapeutic indication according to marketing authorisation

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

Children 6 to 11 years of age with severe atopic dermatitis who are candidates for systemic therapy

Appropriate comparator therapy:

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

- topical glucocorticoids of classes 2 to 3
- tacrolimus (topical)

The authorisation status of the medicinal products must be taken into account.

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

Hint of non-quantifiable additional benefit.

Study results according to endpoints:[1]

Children 6 to 11 years of age with severe atopic dermatitis who are candidates for systemic therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	There were no deaths.
Morbidity	↑	Benefits 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 supplemental AD-1652 study presented.
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:

Morbidity

Endpoint category study 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]

[1] Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A20-123) unless otherwise indicated.

Endpoint category study 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					
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]

Endpoint category study Endpoint	Dupilumab + TCS			Placebo + TCS			Dupilumab + TCS vs Placebo + TCS
	N[d]	Values at the start of the study MV (SD)	Change to day week 52 MV[g] (SE)	N[d]	Values at the start of the study MV (SD)	Change to day week 52 MV[g] (SE)	MD [95%- CI]; p value[e]
CHRONOS (week 52)[a] - age stratum ≥ 18 to < 40 years							
Symptomatology							
patient-reported symptoms - 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

Endpoint category study 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

Endpoint category study 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
complementary: Conjunctivitis (Narrow CMQ)[h,i]	110	15 (13.6)	315	25 (7.9)	1.72 [0.94; 3.14]; 0.079[j]

[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. The values reported in Module 4 E of the dossier are presented.
[b] The response criterion ≥ 4 points was predefined and corresponds to ≥ 15% of the scale span. Thus, as explained in IQWiG's General Methods, the response criterion represents with sufficient certainty a noticeable change for patients.
[c] Logistic regression model, adjusted for randomisation strata
[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] ANCOVA model with baseline values, treatment arm, and randomisation strata as covariates
[f] Lower (decreasing) values mean better symptomatology; negative effects (intervention minus control) mean an advantage for the intervention.
[d] Higher (increasing) values mean better health status; positive effects (intervention minus control) mean an advantage for the intervention.
[h] Total population presented additionally, data presented are from the FDA Medical Review
[i] Post hoc operationalisation on conjunctivitis with 5 PTs (Conjunctivitis narrow CMQ: Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis). The study on conjunctivitis events is based on the increased incidence of conjunctivitis as well as other selected eye disorders during therapy with dupilumab.
[j] 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; MD: Mean difference; MedDRA: Medical dictionary of drug

approval activities; 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 study; RR: relative risk; SCORAD: Scoring Atopic Dermatitis; SD: standard deviation; SE: standard error; SOC: system organ class; TCS: topical glucocorticoids

Supplemental study results presented for AD-1526 study:

Morbidity

Endpoint category study 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[a]
AD-1652 (week 16)[b, c]					
Symptomatology					
Itch - Worst Itch Score (improvement of ≥ 4 points)[d]	118	65 (55.1)	59	6 (10.2)	5.51 [2.54; 11.92]; <0.001
Response (EASI 75)	120	86 (71.7)	59	19 (32.2)	2.19 [1.48; 3.22]; <0.001
Response (EASI 90)	120	52 (43.3)	59	4 (6.8)	6.34 [2.42; 16.66]; <0.001
Response (SCORAD 75)	120	29 (24.2)	59	2 (3.4)	7.08 [1.76; 28.59]; 0.006
Response (SCORAD 90)	120	5 (4.2)	59	0 (0)	5.02 [0.28; 90.00]; 0.223

Endpoint category study Endpoint	Dupilumab + TCS			Placebo + TCS			Dupilumab + TCS vs placebo + TCS
	N[e]	Values at the start of the study MV (SD)	Change to day week 52 MV[g] (SE)	N[e]	Values at the start of the study MV (SD)	Change to day week 52 MV[g] (SE)	MD [95%- CI]; p-value[f]
AD-1652 (week 16)[b, c]							
Symptomatology							
Patient-reported symptomatology-POEM[g, h]	120	21.3 (5.55)	-13.9 (0.67)	59	21.6 (4.82)	-5.1 (0.93)	-8.8 [-10.98; -6.55]; <0.001 Hedges' g: -1.25 [-1.56; -0.93]
Sleep disorders - SCORAD VAS[g]	120	6.8 (2.86)	-4.5 (0.27)	59	6.3 (2.86)	-2.1 (0.37)	-2.3 [-3.18; -1.43]; <0.001 Hedges' g: -0.83 [-1.14; -0.51]
Health status							
EQ-5D VAS					-[i]		

Health-related quality of life

Endpoint category study 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[a]
AD-1652 (week 16)[b, c]					
Health-related quality of life					
CDLQI (0 or 1)[j]	120	36 (30.0)	59	2 (3.4)	8.80 [2.20; 35.28]; 0.002

Side effects

Endpoint category study 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[a]
AD-1652 (week 16[j])[b, c]					
Side effects					
Eye disorders (SOC, AEs)[k]	120	7 (5.8)	120[l]	8 (6,7)[l]	0.88 [0.33; 2.34]; 0.864[m]
Complementary: Conjunctivitis or blepharitis (Narrow CMQ)[k,n]	120	8 (6.7)	120[l]	5 (4,2)[l]	1.60 [0.54; 4.75]; 0.529[m]

[a] logistic regression model, adjusted for region and weight at baseline
[b] Unless otherwise stated, the data presented are from Module 4 E of the dossier. The pharmaceutical company presents in his dossier exclusively results of the Q4W treatment scheme with dupilumab in comparison with the Q4W treatment regimen with placebo of patients < 60 kg body weight. The study included 10 children with a bodyweight ≥ 60 kg; information on how they were distributed among the study arms is not available.
[c] The mailing of unblinded packing lists potentially unblinded 23 patients in the Q4W treatment scheme (< 60 kg body weight). In order to test for a potential influence on the study results, the company performs sensitivity analyses on selected efficacy endpoints using a modified Full Analysis Set (mFAS). There were no relevant differences in the results for the endpoints of morbidity and health-related quality of life between the FAS and mFAS analyses. The FAS evaluations are presented.
[d] The response criterion ≥ 4 points was predefined and corresponds to ≥ 15% of the scale span. Thus, as explained in IQWiG's General Methods, the response criterion represents with sufficient certainty a noticeable change for patients.
[e] Number of patients who were taken into account in the evaluation for calculating the effect estimate; the values start of study can be based on other patient numbers.
[f] ANCOVA model with baseline values, treatment arm, and randomisation strata as covariates
[g] Lower (decreasing) values mean better symptomatology; negative effects (intervention minus control) mean an advantage for the intervention.
[h] According to the study protocol, the questionnaire version for completion by legal guardians was used. However, the version of the questionnaire is not included in the study protocol. It can be assumed that the questionnaire was filled in jointly by the child and the parent or guardian - as for example in provided when the child is old enough to understand the questions. This is assumed to be true for children 6 years and older included in the study.
[i] Endpoint not surveyed
[j] In the AD-1652 study, the CDLQI was used instead of the DLQI. This differs in particular in that the question on sexuality in the DLQI has been replaced by a question on sleep. In the present case, this is of minor relevance, as only patients with a CDLQI or DLQI of 0 or 1 are presented.
[k] The data presented are taken from the European Public Assessment Report
[l] Data refer to all patients who received placebo (Q2W and Q4W treatment scheme).
[m] IQWiG calculations 95% CI asymptotic, unconditional exact test (CSZ method)
[n] operationalisation for conjunctivitis with 5 PTs as part of the study (Conjunctivitis narrow SMQ: Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis).

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 of drug approval 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 study; RR: relative risk; SCORAD: Scoring Atopic Dermatitis; SD: standard deviation; SE: standard error; SOC: System organ class; TCS: topical glucocorticoids; VAS: visual analogue scale

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

Children 6 to 11 years of age with severe atopic dermatitis who are candidates for systemic therapy

approx. 9,700 to 14,100 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: 4 May 2021):
https://www.ema.europa.eu/documents/product-information/dupixent-epar-product-information_de.pdf

In patients in whom no therapeutic benefit can be demonstrated after 16 weeks of treatment, discontinuation of treatment should be considered. Some patients with an initial partial response may benefit from continued treatment beyond 16 weeks.

4. Treatment costs

Annual treatment costs:

Children 6 to 11 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	€ 8,863.47 - € 17,795.11
Appropriate comparator therapy:	
Hydrocortisone butyrate[2]	Patient-individual
Methylprednisolone[3]	Patient-individual
Tacrolimus	Patient-individual

Costs after deduction of statutory rebates (LAUER-TAXE®, as last revised: 15 June 2021)

Costs for additionally required SHI services: not applicable

[2] Hydrocortisone butyrate is exemplified for the topical glucocorticoids of class II.
[3] Methylprednisolone is exemplified for the topical glucocorticoids of class III.