Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Dupilumab (New Therapeutic Indication: Chronic Dermatitis, Adolescent Patients 12 to < 18 Years)

of 20 February 2020

At its session on 20 February 2020, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (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 on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of dupilumab in accordance with the resolution of 17 May 2018:

Dupilumab

Resolution of: 20 February 2020
Entry into force on: 20 February 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 1 August 2019):

Dupixent is indicated for the treatment of moderate-to-severe atopic dermatitis (AD) in adolescents 12 years and older who are candidates for systemic therapy.

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

Treatment of moderate-to-severe atopic dermatitis in adolescents 12 years and older who are candidates for systemic therapy

Appropriate comparator therapy:

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

- topical class 2 to 4 glucocorticoids
- tacrolimus (topical)
- cyclosporine

The respective marketing authorisation status of the medicinal product must be taken into account.

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

Hint for a non-quantifiable additional benefit.

Study results according to endpoints:[1]

Treatment of moderate-to-severe atopic dermatitis in adolescents 12 years and older who are candidates for systemic therapy

Appropriation of the results of the age group ≥ 18 to < 40 years of the CHRONOS study to the age group adolescents:

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[a]
CHRONOS (week 52) – age range ≥ 18 to < 40 years					
Morbidity					
Symptomatology					
Itching – peak pruritus NRS improvement by ≥ 4 points	50	31 (62.0)	182	59 (32.4)	1.90 [1.41; 2.56]; < 0.001
Response (EASI 75)	52	35 (67.3)	189	89 (47.1)	1.39 [1.09; 1.76]; 0.008
Response (EASI 90)	52	26 (50.0)	189	54 (28.6)	1.63 [1.15; 2.29]; 0.006
Response (SCORAD 75)	52	19 (36.5)	188	33 (17.6)	1.89 [1.19; 3.00]; 0.007
Response (SCORAD 90)	52	7 (13.5)	188	14 (7.4)	1.66 [0.71; 3.87]; 0.242
Health-related quality of life					
DLQI (0 or 1)	52	23 (44.2)	189	30 (15.9)	2.67 [1.71; 4.17]; < 0.001
Side effects					
Eye disorders (SOC, AEs)	55	17 (30.9)	189	22 (11.6)	2.66 [1.52; 4.64][b]; 0.001[c]
in addition: Conjunctivitis or blepharitis[d] (PT, AEs)	55	9 (16.4)	189	14 (7.4)	2.21 [1.01; 4.84][b]; 0.047[c]

a: Unless otherwise stated; RR, CI and p-value from logistic regression adjusted for severity of atopic dermatitis (IGA) at start of study and for region
b: RR normal approximation; CI asymptomatic
c: Calculation by the IQWiG, unconditional exact test (CSZ method)
d: PTs for conjunctivitis or blepharitis that developed during the course of the study

DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; n.s.: not specified; CI: confidence interval; IGA: Investigator's Global Assessment; n: number of patients with (at least 1) event; N: number of patients evaluated; NRS: Numerical Rating Scale; PT: Preferred Term; RCT: Randomised Controlled Study; RR: Relative Risk; SCORAD: SCORing Atopic Dermatitis; SOC: System Organ Class; TCS: topical corticosteroids; AE: Adverse Event; vs: versus

[1] Data from the dossier evaluation of the IQWiG (A19-75) and the addendum (A20-01) unless otherwise indicated.

Study endpoint category Endpoint	Dupilumab + TCS			Placebo + TCS			Dupilumab + TCS vs placebo + TCS
	N [a]	Values at start of study MV (SD)	Change at week 24 MV (SE)[b]	N[a]	Values at start of study MV (SD)	Change at week 24 MV (SE)[b]	MD [95% CI]; p value[b]
CHRONOS (week 52) – age range ≥ 18 to < 40 years							
Morbidity							
Symptomatology							
Patient-Oriented Eczema Measure (POEM)[c,d]	52	20.54 (5.15)	-12.57 (0.93)	189	20.44 (6.00)	-7.09 (0.51)	-5.47 [-7.54; -3.41]; < 0.001 Hedges' g[e]: -0.85 [-1.17; -0.53]
Sleep disturbances – SCORAD VAS[c, d]	52	5.38 (3.31)	-4.09 (0.26)	189	4.94 (3.22)	-2.92 (0.14)	-1.17 [-1.73; -0.61]; < 0.001 Hedges' g[e]: -0.66 [-0.98; -0.34]
Health status							
EQ-5D VAS[c,f]	52	58.28 (22.14)	19.91 (2.27)	189	55.23 (22.87)	15.33 (1.22)	4.58 [-0.38; 9.53]; 0.070

a: Number of patients who were taken into account in the evaluation for the calculation of the effect estimator; the values at the start of study (at other times, if necessary) can be based on other patient figures.

b: Calculated using the ANCOVA model, with treatment, value at start of study, region and severity of atopic dermatitis (IGA) as factors

c: Replacement of missing values using MI

d: A high value indicates severe symptoms; a negative group difference indicates an advantage for dupilumab.

e: IQWIG calculation based on mean difference and CI

f: Higher values indicate a better health status; a positive group difference indicates an advantage for dupilumab.

ANCOVA: covariance analysis; EQ-5D: European Quality of Life – 5 Dimensions; IGA: Investigator's Global Assessment; n.s.: not specified; CI: confidence interval; MD: mean difference; MI: multiple imputation; MV: mean value; N: number of patients evaluated; POEM: Patient-Oriented Eczema Measure; RCT: randomised control trial; SCORAD: SCORing Atopic Dermatitis; SD: standard deviation; SE: standard error; TCS: topical corticosteroids; VAS: visual analogue scale; vs: versus

Supplementary presented study results of the AD-1526 study:

Study Endpoint Category Endpoint	Dupilumab		Placebo		Dupilumab vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95 % CI]; p value[a]
AD-1526 (week 16)					
Morbidity					
Symptomatology					
Itching −peak pruritus – NRS Improvement by ≥ 4 points	82	37 (45.1)	84	14 (16.7)	2.76 [1.62; 4.70]; < 0.001
Response (EASI 75)	82	37 (45.1)	85	13 (15.3)	2.89 [1.66; 5.01]; < 0.001
Response (EASI 90)	82	19 (23.2)	85	3 (3.5)	6.44 [1.99; 20.84]; 0.002
Response (SCORAD 75)	82	13 (15.9)	85	4 (4.7)	3.41 [1.16; 9.99]; 0.026
Response (SCORAD 90)	82	2 (2.4)	85	1 (1.2)	2.07 [0.19; 22.43]; 0.548
Health-related quality of life					
CDLQI (0 or 1)[b]	82	20 (24.4)	84	6 (7.1)	3.39 [1.44; 8.01]; 0.005
Side effects					
Eye disorders (SOC, AEs)	82	6 (7.3)	85	7 (8.2)	0.89 [0.31; 2.53]; 0.859[c]
Conjunctivitis or blepharitis[d] (PT, AEs) (presented as a supplement)	82	8 (9.8)	85	5 (5.9)	1.66 [0.56; 4.89][e]; 0.529[f]

a: Unless otherwise indicated; RR, CI and p-value from logistic regression are adjusted respectively for severity of atopic dermatitis (IGA) and weight at start of study
b: In study AD-1526, CDLQI was employed instead of DLQI. This differs, specifically, in that the DLQI's question on sexuality has been replaced by a question on sleep. In the present case this is of secondary relevance, since only patients with a CDLQI or DLQI of 0 or 1 are presented.
c: IQWiG calculation of RR, CI (asymptomatic) and p-value
d: PTs for conjunctivitis or blepharitis that developed during the course of the study under e: RR normal approximation; CI asymptomatic
f: IQWiG calculation, unconditional exact test

CDLQI: Children's Dermatology Life Quality Index; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; CI: confidence interval; IGA: Investigator's Global Assessment; n: number of patients with (at least 1) event; N: number of patients evaluated; NRS: Numerical Rating Scale; PT: preferred term; RCT: randomised controlled trial; RR: relative risk;
SCORAD: SCORing Atopic Dermatitis; SOC: system organ class; AE: adverse event; vs: versus; ACT appropriate comparator therapy

Study Endpoint Category Endpoint	Dupilumab			Placebo			Dupilumab vs placebo
	N[a]	Values at start of study MV (SD)	Change at week 16 MV (SE)[b]	N[a]	Values at start of study MV (SD)	Change at week 16 MV (SE)[b]	MD [95 % CI]; p value[b]
AD-1526 (week 16)							
Morbidity							
Symptomatology							
Patient-Oriented Eczema Measure (POEM)[c,d]	82	21.0 (5.0)	-10.1 (0.77)	85	21.1 (5.9)	-4.9 (0.75)	-5.28 [-7.39; -3.17]; < 0.001 Hedges' g[e]: -0.76 [-1.07; -0.44]
Sleep disturbances – SCORAD VAS[c, d]	82	5.4 (3.4)	-3.6 (0.30)	85	5.6 (3.1)	-2.04 (0.30)	-1.52 [-2.35; -0.70]; < 0.001 Hedges' g[e]: -0.56 [-0.87; -0.25]
Health status							
(EQ-5D VAS)[f]					-[g]		

a: Number of patients who were taken into account in the evaluation for the calculation of the effect estimator; the values at the start of study (at other times, if necessary) can be based on other patient figures.

b: Calculated using the ANCOVA model; treatment, value at start of study, weight and severity of atopic dermatitis (IGA) as factors

c: Replacement of missing values using MI

d: A high value indicates severe symptoms; a negative group difference indicates an advantage for dupilumab.

e: IQWIG calculation based on mean difference and CI

f: Higher values indicate a better health status; a positive group difference indicates an advantage for dupilumab.

g: Endpoint not recorded

ANCOVA: covariance analysis; EQ-5D: European Quality of Life – 5 Dimensions; CI: confidence interval; IGA: Investigator's Global Assessment; MD: mean difference; MI: multiple imputation; MV: mean value;

N: number of patients evaluated; POEM: Patient-Oriented Eczema Measure; RCT: randomised control trial; SCORAD: SCORing Atopic Dermatitis; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs: versus; ACT appropriate comparator therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect / risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↑	Benefits for the symptoms itching and sleep disturbances, patient-reported symptoms and improvement of EASI score by 75% and 90% and improvement of SCORAD score by 75%.
Health-related quality of life	↑	Benefit on reaching a DLQI of 0 or 1.
Side effects	↓	Disadvantages in eye diseases.

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

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

approx. 5300 to 10600 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: 25 November 2019):
https://www.ema.europa.eu/documents/product-information/dupixent-epar-product-information_en.pdf

In patients who do not respond 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:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Dupilumab	€ 19,058.35
Appropriate comparator therapy:	
Topical therapies	
Hydrocortisone butyrate[2]	Different for each individual patient
Methyl prednisolone[3]	Different for each individual patient
Clobetasol[4]	Different for each individual patient
Tacrolimus	Different for each individual patient
Systemic therapies	
Cyclosporine	Different for each individual patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2020

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 20 February 2020.

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

Berlin, 20 February 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken

2 Hydrocortisone butyrate is depicted as a topical class II glucocorticoid exemplar.
3 Methyl prednisolone is depicted as a topical class III glucocorticoid exemplar.
4 Clobetasol is depicted as a topical class IV glucocorticoid exemplar.