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: treatment of moderate-to-severe prurigo nodularis)

of 5 October 2023

At its session on 5 October 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 severe atopic dermatitis, 6 months to 5 years":**

Courtesy translation – only the German version is legally binding.

Dupilumab

Resolution of: 5 October 2023
Entry into force on: 5 October 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 12 December 2022):

Dupixent is indicated for the treatment of adults with moderate-to-severe prurigo nodularis (PN) who are candidates for systemic therapy.

Therapeutic indication of the resolution (resolution of 5 October 2023):

See new therapeutic indication according to marketing authorisation.

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

Adults with moderate-to-severe prurigo nodularis (PN) who are candidates for systemic therapy

Appropriate comparator therapy:

- Best supportive care

  Best supportive care (BSC) is defined as the therapy that provides the best possible, patient-individual, optimised supportive treatment to alleviate symptoms and improve quality of life.

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

Hint for a non-quantifiable additional benefit.

Study results according to endpoints:[1]

Adults with moderate-to-severe prurigo nodularis (PN) who are candidates for systemic therapy

1 Data from the dossier assessment of the IQWiG (A23-24) and from the addendum (A23-82), unless otherwise indicated.

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Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↑	Meta-analysis: Advantages for lesions, anxiety symptomatology, depressive symptomatology and health status. PRIME study: Advantages for symptoms of itching, skin pain and sleep quality.
Health-related quality of life	↑	Meta-analysis: Advantage in achieving a DLQI of 0 or 1.
Side effects	↑	Advantage in the endpoint of discontinuation due to AEs.

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

PRIME and PRIME2 studies (RCTs over 24 weeks; dupilumab versus placebo - each in addition to background therapy) and their meta-analysis

Mortality

Endpoint Study	Dupilumab		Placebo		Dupilumab vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Overall mortality[b]					
PRIME	75	0 (0)	76	0 (0)	-
PRIME2	78	0 (0)	82	0 (0)	-[c]

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Morbidity

Endpoint/ scale study	Dupilumab		Placebo		Dupilumab vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Symptomatology					
Itching - WI-NRS (improvement by ≥ 4 points)[d, e]					
PRIME	75	48 (64.0)	76	19 (25.0)	2.77 [1.71; 4.48]; < 0.001
PRIME2	No usable data available[c]				
Total					-[c]
Skin pain NRS (improvement ≥ 1.5 points)[f, e]					
PRIME	75	63 (84.0)	76	39 (51.3)	1.62 [1.25; 2.09]; < 0.001
PRIME2	No usable data available[c]				
Total					-[c]
Sleep quality NRS (improvement ≥ 1.5 points)[g, e]					
PRIME	75	45 (60.0)	76	24 (31.6)	2.12 [1.41; 3.19]; < 0.001
PRIME2	No usable data available[c]				
Total					-[c]
Lesions[h, e]					
PRIME	75	11 (14.7)	76	2 (2.6)	6.03 [1.24; 29.34]; 0.026
PRIME2	78	17 (21.8)	82	3 (3.7)	–[c]
Total	153	28 (18.3)	158	5 (3.2)	6.69 [2.22; 20.17]; < 0.001
Anxiety symptomatology - HADS-A (improvement ≥ 3.15 points)[i, e]					
PRIME	75	29 (38.7)	76	16 (21.1)	2.02 [1.17; 3.50]; 0.0121
PRIME2	78	36 (46.2)	82	17 (20.7)	–[c]
Total	153	65 (42.5)	158	33 (20.9)	2.08 [1.44; 3.00]; < 0.001

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Endpoint/ scale study	Dupilumab		Placebo		Dupilumab vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Depressive symptomatology - HADS-D (improvement ≥ 3.15 points)[i, e]					
PRIME	75	21 (28)	76	12 (15.8)	1.86 [0.93; 3.74]; 0.081
PRIME2	78	24 (30.8)	82	12 (14.6)	–[c]
Total	153	45 (29.4)	158	24 (15.2)	2.12 [1.32; 3.40]; 0.002
Health status					
PGIC[j, d]					
PRIME	75	64 (85.3)	76	28 (36.8)	2.25 [1.66; 3.04]; < 0.001
PRIME2	78	61 (78.2)	82	31 (37.8)	–[c]
Total	153	125 (81.7)	158	59 (37.3)	2.28 [1.82; 2.86]; < 0.001
EQ-5D VAS (improvement ≥ 15 points)[k, e]					
PRIME	75	31 (41.3)	76	13 (17.1)	2.50 [1.30; 4.82]; 0.006
PRIME2	78	35 (44.9)	82	23 (28.0)	–[c]
Total	153	66 (43.1)	158	36 (22.8)	2.01 [1.39; 2.92]; < 0.001

Endpoint/ scale Study	Dupilumab			Placebo			Dupilumab vs placebo
	N[m]	Values at start of study MV (SD)	Change at week 24 N[n]; MV[o] (SE)	N[m]	Values at start of study MV (SD)	Change at week 24 N[n]; MV[o] (SE)	MD[o] [95% CI]; p value
Health status (PGIS)[p]							
PRIME	75	3.28 (0.45)	74; -1.64 (0.17)	76	3.29 (0.46)	65; -0.78 (0.18)	-0.75 [-0.99; -0.50]; < 0.001
PRIME2	78	3.74 (0.55)	75; -1.63 (0.18)	82	3.72 (0.48)	62; -0.89 (0.17)	-0.74 [-1.03; -0.44]; < 0.001
Total	153	3.71 (0.52)	149; –1.64 (0.1)	158	3.65 (0.49)	127; -0.93 (0.1)	-0.71 [-0.90; -0.52]; < 0.001

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Endpoint/ scale Study	Dupilumab			Placebo			Dupilumab vs placebo
	N[m]	Values at start of study MV (SD)	Change at week 24 N[n]; MV[o] (SE)	N[m]	Values at start of study MV (SD)	Change at week 24 N[n]; MV[o] (SE)	MD[o] [95% CI]; p value
							SMD: -0.88 [-1.12; -0.65]

Health-related quality of life

Endpoint/ scale study	Dupilumab		Placebo		Dupilumab vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Health-related quality of life					
DLQI (0 or 1)[l, e]					
PRIME	75	20 (26.7)	76	13 (17.1)	1.52 [0.78; 2.96]; 0.219
PRIME2	78	17 (21.8)	82	4 (4.9)	–[c]
Total	153	37 (24.2)	158	17 (10.8)	2.39 [1.31; 4.34]; 0.004

Side effects

Endpoint/ scale Study	Dupilumab		Placebo		Dupilumab vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
AEs (presented additionally)[q]					
PRIME	75	52 (69.3)	75	44 (58.7)	–
PRIME2	77	47 (61)	82	44 (53.7)	–
SAEs[q]					
PRIME	75	5 (6.7)	75	7 (9.3)	0.71 [0.24; 2.17]; 0.551
PRIME2	77	2 (2.6)	82	4 (4.9)	–[c]

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Endpoint/ scale Study	Dupilumab		Placebo		Dupilumab vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]
Total	152	7 (4.6)	157	11 (7)	0.65 [0.26; 1.64]; 0.361
Discontinuation due to AEs					
PRIME	75	0 (0)	75	3 (4)	0.13[r] [0.01; 1.29]; 0.081
PRIME2	77	0 (0)	82	1 (1.2)	–[c]
Total	152	0 (0)	157	4 (2.5)	0.14[r] [0.02; 0.98]; 0.048

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Endpoint/ scale Study	Dupilumab		Placebo		Dupilumab vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value[a]

a. RR [95% CI], p value for the individual studies from Cochran-Mantel-Haenszel test, stratified by atopic history (atopic or non-atopic), TCS/TCI treatment (yes or no), region, antidepressants at baseline (yes or no); for IPD meta-analysis, same model with the additional stratification factor study (PRIME or PRIME2).
b. Fatalities were recorded as part of adverse events.
c. No usable data for the PRIME2 study or for the IPD meta-analysis of both PRIME and PRIME2 studies.
d. Percentage of patients with a decrease in the respective score by ≥ 4 points at week 24 compared to start of study, with a scale range of 0 to 10. Lower (decreasing) values mean an improvement of symptomatology.
e. For the end of treatment (week 24), missing observations were replaced by a non-responder imputation (NRI).
f. Percentage of patients with a decrease in the respective score by ≥ 1.5 points at week 24 compared to start of study, with a scale range of 0 to 10. Lower (decreasing) values mean an improvement of symptomatology.
g. Lower (decreasing) values mean better health status; negative effects (intervention minus control) mean an advantage for the intervention (scale range 1 to 4).
h. Percentage of patients with 100% healed lesions at week 24.
i. Percentage of patients with a decrease (in anxiety [HADS-A] or depression [HADS-D] score) by ≥ 3.15 points at week 24 compared to start of study, with a scale range of 0 to 21. Lower (decreasing) values mean an improvement of symptomatology.
j. Percentage of patients who rated their health status as much better or better at week 24 compared to start of study.
k. Percentage of patients with an increase in the respective score by ≥ 15 points at week 24 compared to start of study, with a scale range of 0 to 100. Higher (increasing) values mean an improvement of health status.
l. Percentage of patients achieving a DLQI of 0 or 1 (no impairment of quality of life) at week 24.
m. Number of patients who were taken into account in the evaluation for calculating the effect estimate; the values at week 24 are based on other patient numbers.
n. Number of patients with values at week 24.
o. ANCOVA evaluation of the ITT population with baseline value, treatment group, atopic history (atopic or non-atopic), TCS/TCI treatment (yes or no), region, antidepressants at baseline (yes or no) and study indicator (PRIME or PRIME2) as covariates. Missing values were replaced by means of multiple imputation (MI).
p. Lower (decreasing) values mean better health status; negative effects (intervention minus control) mean an advantage for the intervention (scale range 1 to 4).
q. Without the following disease-related events: LLT prurigo nodularis and LLT prurigo nodularis flare
r. Peto-OR as estimator for the relative risk; the p value was determined via a normal approximation.

ANCOVA: analysis of covariance; CMQ: Customized MedDRA query; DLQI: Dermatology Life Quality Index; HADS: Hospital Anxiety and Depression Scale; IPD: individual patient data; ITT: intention to treat; CI: confidence interval; LLT: lowest level term; MD: adjusted mean difference; MV: adjusted mean value; n: number of patients with (at least 1) event; N: number of patients evaluated; NRS: Numerical Rating Scale; OR: odds ratio; PGIC: Patient Global Impression of Change; PT: preferred term; RCT: randomised controlled trial; RR: relative risk; SD: standard deviation; SE: standard error; SMD: standardised mean difference; SOC: system organ class, SAE: serious adverse event; TCI: topical calcineurin inhibitors; TCS: topical glucocorticoids; AE: adverse event; VAS: visual analogue scale; WI-NRS: Worst Itching Intensity Numerical Rating Scale

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

Adults with moderate-to-severe prurigo nodularis (PN) who are candidates for systemic therapy

approx. 3,500 – 4,800 patients

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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: 26 June 2023):

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

4. Treatment costs

Annual treatment costs:

Adults with moderate-to-severe prurigo nodularis (PN) who are candidates for systemic therapy.

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Dupilumab	€ 15,675.66
Best supportive care	Different from patient to patient
Appropriate comparator therapy:	
Best supportive care	Different from patient to patient

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 September 2023

Costs for additionally required SHI services: not applicable

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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:

Adults with moderate-to-severe prurigo nodularis (PN) who are candidates for systemic therapy

- 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.

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 5 October 2023.

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

Berlin, 5 October 2023

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

Prof. Hecken

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