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
Mepolizumab (new therapeutic indication: hypereosinophilic syndrome (HES))

of 19 May 2022

At its session on 19 May 2022, 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. 4 to the information on the benefit assessment of Mepolizumab in accordance with the resolution of 19 May 2022 (new therapeutic indication: eosinophilic granulomatosis with polyangiitis):

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Mepolizumab

Resolution of: 19 May 2022
Entry into force on: 19 May 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 12 November 2021):

Nucala is indicated as an add-on treatment for adult patients with inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause.

Therapeutic indication of the resolution (resolution of 19 May 2022):

See new therapeutic indication according to marketing authorisation.

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

Adults with inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause

Appropriate comparator therapy:

Therapy according to doctor's instructions

Extent and probability of the additional benefit of Mepolizumab compared to therapy according to the doctor's instructions:

Hint of a considerable additional benefit

Study results according to endpoints:[1]

Adults with inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause

[1] Data from the dossier assessment of the IQWiG (A21-152) and from the addendum (A22-45), 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 statistically significant difference
Morbidity	↑	Advantages in the endpoints of clinically manifested HES relapses and activity impairment
Health-related quality of life	↑	Advantage in the physical component score of the SF-36
Side effects	↔	No statistically significant difference

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

RCT 200622 study: Mepolizumab vs placebo (each in addition to standard therapy), 32 weeks

Mortality

200622 study Endpoint	Mepolizumab + standard therapy		Placebo + standard therapy		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI]; p value
Overall mortality	54	1 (2)	54	0 (0)	–[a]; 0.528[b]

Morbidity

200622 study Endpoint	Mepolizumab + standard therapy		Placebo + standard therapy		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI]; p value
Clinically manifested HES relapses[c]	54	13 (24)	54	25 (46)	0.52 [0.28; 0.94]; 0.016[d]
Fatigue of highest intensity (BFI item 3)[e, f]	54	18 (33)	54	11 (20)	0.61 [0.30; 1.17]; 0.149[g, h]

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Fatigue intensity / Fatigue impairment (BFI total score)[f, i]	54	17 (31)	54	10 (19)	0.59 [0.28; 1.16]; 0.131[g, h]
Patient-assessed treatment response (RTS)	No usable data available				
Patient-assessed symptom severity (SSR)	No usable data available				

200622 study Endpoint	Mepolizumab + standard therapy		Placebo + standard therapy		Intervention vs control
	Values at the start of study MV (SD)	Change at week 32 MV[k] (SE)	Values at the start of study MV (SD)	Change at week 32 MV[k] (SE)	MD [95% CI] [k]; p value
	N[j] = n/s		N[j] = n/s		
Severity of HES symptoms (HES-DS)[l]					
Muscle / joint pain	3.86 (2.49)	-1.03 (0.27)	3.08 (2.68)	-0.27 (0.27)	-0.76 [-1.52; 0.01]; 0.052
Chills or sweats	2.65 (2.82)	-1.19 (0.24)	1.98 (2.37)	-0.41 (0.25)	-0.78 [-1.47; -0.09]; 0.026 SMD: -0.46 [-0.86; -0.05]
Abdominal pain or flatulence	3.12 (2.84)	-0.75 (0.24)	2.63 (2.41)	-0.05 (0.25)	-0.70 [-1.39; 0.00]; 0.049 SMD: -0.40 [-0.81; 0.00]
Breathing symptoms	4.08 (3.22)	-1.73 (0.27)	3.23 (2.80)	-0.82 (0.28)	-0.91 [-1.68; -0.13]; 0.022 SMD: -0.47 [-0.88; -0.07]
Symptoms of the nose or sinus cavity	3.51 (3.04)	-1.07 (0.27)	2.90 (2.83)	-0.32 (0.28)	-0.75 [-1.53; 0.03] 0.059

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200622 study Endpoint	Mepolizumab + standard therapy		Placebo + standard therapy		Intervention vs control
	Values at the start of study MV (SD)	Change at week 32 MV[k] (SE)	Values at the start of study MV (SD)	Change at week 32 MV[k] (SE)	MD [95% CI] [k]; p value
	N[j] = n/s		N[j] = n/s		
Skin symptoms	2.94 (2.80)	-0.66 (0.28)	3.37 (3.14)	-0.41 (0.28)	-0.25 [-1.04; 0.53]; 0.522
Activity impairment					
Activity impairment (WPAI question 6) (%)[m]	46.3 (30.49)	-20.20 (3.47)	40.4 (28.61)	-3.61 (3.46)	−16.59 [−26.39; −6.80]; 0.001 SMD: -0.74 [-1.18; -0.29]

Health-related quality of life

200622 study Endpoint	Mepolizumab + standard therapy		Placebo + standard therapy		Intervention vs control
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	RR [95% CI]; p value
SF-36					
Physical component score (PCS)[f, n]	54	16 (39)	54	4 (7)	0.25 [0.07; 0.69]; 0.003[g, h]
Mental component score (MCS)[f, o]	54	14 (26)	54	6 (11)	0.43 [0.13; 1.03]; 0.051[g, h]

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Side effects

200622 study Endpoint	Mepolizumab + standard therapy		Placebo + standard therapy		Intervention vs control
	N	Median in months [95% CI] *Patients with event n (%)*	N	Median in months [95% CI] *Patients with event n (%)*	Effect estimator [95% CI] p value Absolute difference (AD)[a]
AEs (presented additionally)	54	48 (89)	54	47 (87)	-
SAEs[p]	54	9 (17)	54	8 (15)	1.13 [0.45; 3.22]; 0.870[g]
Discontinuation due to AEs	54	0 (0)	54	2 (4)	0.2 [0.01; 4.07]; 0.209[d]

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a. Effect estimate and 95% CI cannot be interpreted meaningfully.
b. p value: IQWiG calculation, unconditional exact test (CSZ method)
c. Patients with ≥ 1 HES relapse or premature study discontinuation; the following discrepant information is found in Module 4 C: patients with ≥ 1 HES relapse or premature therapy discontinuation; in contrast to the information provided by the company in Module 4 C of the dossier, it is clear from the study documents that analyses on patients with ≥ 1 HES relapse or premature study discontinuation are presented in Module 4 C. Due to the small number of patients affected (n = 1 in the intervention arm and n = 2 in the control arm), the consideration of patients without HES relapse with premature study discontinuation has no relevant influence on the results overall.
d. CI (asymptotic) IQWiG calculation; in the case of 0 events in a study arm, the correction factor 0.5 was used in both study arms when calculating effect and CI; p value: IQWiG calculation, unconditional exact test (CSZ method)
e. Percentage of patients with improvement: decrease by ≥ 1.5 points (corresponds to ≥ 15% of the scale range from 0 to 10) in the most intense level of fatigue in the past 24 hours (BFI item 3) at week 32
f. Missing values are replaced by the pharmaceutical company as non-responders
g. Unconditional exact CI, calculated by inverting two separate one-sided tests based on the score statistic; p value: IQWiG calculation, unconditional exact test (CSZ method);
h. Data based on comparison of placebo + standard therapy vs mepolizumab + standard therapy
i. Percentage of patients with improvement: decrease by ≥ 1.5 points (corresponds to ≥ 15 % of the scale range from 0 to 10) in the BFI total score at week 32
j. Number of patients included in the evaluation for the calculation of the effect estimate
k. MMRM baseline value, OCS dose at baseline, region, treatment group and visit, and interaction terms for visit and baseline value and visit and treatment group; effect represents the difference in changes between treatment groups from the start of the study to week 32.
l. Lower (decreasing) values mean better symptomatology; negative effects (intervention minus control) mean an advantage for the intervention (scale range 0 to 10).
m. Percentage impairment; a lower percentage means a lower activity impairment; negative effects (intervention minus control) mean an advantage for the intervention (scale range 0 to 100)
n. Percentage of patients with improvement: increase in PCS score by ≥ 9.4 points at week 32 compared to start of the study (corresponds to 15% of the scale range; normalised scale with a minimum of approximately 7 and a maximum of approximately 70); no data available on the subscales of the SF-36
o. Percentage of patients with improvement: increase in MCS score by ≥ 9.6 points at week 32 compared to the start of the study (corresponds to 15% of the scale range; normalised scale with a minimum of approximately 6 and a maximum of approximately 70); no data available on the subscales of the SF-36v2
p. Without deaths

BFI: Brief Fatigue Inventory; HES: hypereosinophilic syndrome; HES-DS: HES-Daily Symptoms; CI: confidence interval; MCS: mental component score; MV: Mean Value; n: number of patients with (at least 1) event; N: number of patients evaluated; OCS: oral corticosteroid; PCS: physical component score; RCT: randomised controlled trial; RR: relative risk; RTS: Response to Therapy Score; SD: Standard Deviation; SE: Standard Error; SF-36v2: Short Form-36 Health Survey Version 2; SMD: Standardised Mean difference; SSR: Subject-Rated Symptom Severity; SAE: Serious Adverse Event; AE: Adverse Event

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

Adults with inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause

approx. 100 to 400 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 Nucala (active ingredient: mepolizumab) at the following publicly accessible link (last access: 9 February 2022):

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

Treatment with mepolizumab should only be initiated and monitored by doctors experienced in treating hypereosinophilic syndrome.

Mepolizumab is intended for long-term treatment. The need for continued therapy should be reviewed at least once a year. Patients who develop life-threatening manifestations of HES should also be evaluated for the need for continued therapy as mepolizumab has not been studied in this patient group.

Patients who were FIP1L1-PDGFRα-kinase positive were excluded from the study.

4. Treatment costs

Annual treatment costs:

Adults with inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Mepolizumab	€ 48,491.56
Therapy according to doctor's instructions	No data available
Appropriate comparator therapy:	
Therapy according to doctor's instructions	No data available

Costs after deduction of statutory rebates (LAUER-TAXE® as last revised: 1 May 2022)

Costs for additionally required SHI services: not applicable

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II. The resolution will enter into force on the day of its publication on the website of the G-BA on 19 May 2022.

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

Berlin, 19 May 2022

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

Prof. Hecken

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