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
Rozanolixizumab (myasthenia gravis, AChR antibody+, MuSK antibody+)

of 15 August 2024

At its session on 15 August 2024, 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. Annex XII shall be amended in alphabetical order to include the active ingredient Rozanolixizumab as follows:

Rozanolixizumab

Resolution of: 15 August 2024
Entry into force on: 15 August 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 5 January 2024):

Rystiggo is indicated as an add-on to standard therapy for the treatment of generalised myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive.

Therapeutic indication of the resolution (resolution of 15 August 2024):

Therapeutic indication according to marketing authorisation.

1. Extent of the additional benefit and significance of the evidence

Rozanolixizumab is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5 Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5 Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

a) Adults with anti-AChR antibody-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy

Extent of the additional benefit and significance of the evidence of rozanolixizumab as an add-on therapy:

Hint for a considerable additional benefit

b) Adults with anti-MuSK antibody-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy

Extent of the additional benefit and significance of the evidence of rozanolixizumab:

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification

Study results according to endpoints:[1]

a) Adults with anti-AChR antibody-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↑	Advantages in disease-specific symptomatology.
Health-related quality of life	↑	Advantage in myasthenia gravis quality of life 15-item scale score.
Side effects	↔	No relevant differences for the benefit assessment.
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		

MG0003 study: Phase III RCT, rozanolixizumab versus placebo, 1 treatment cycle (42 days) + 8 weeks follow-up, total population

Mortality

Endpoint	Rozanolixizumab n = 66	Placebo n = 67
	Patients with event n (%)	Patients with event n (%)
Mortality		
	No deaths have occurred.	

[1] Data from the dossier assessment of the G-BA (published on 3. Juni 2024), and from the amendment to the dossier assessment from 25 July 2024, unless otherwise indicated.

Morbidity

Endpoint	Rozanolixizumab n = 66	Placebo n = 67	Rozanolixizumab vs placebo
	Patients with event n (%)	Patients with event n (%)	RR [95% CI][a]; p value[b]
Disease-specific symptomatology - Myasthenia Gravis (MG) Activities of Daily Living (ADL)[c]			
One-time improvement of the MG-ADL by ≥ 4 points on day 43	30 (45.5)	10 (14.9)	3.35 [1.80; 6.23][d]; <0.001
Disease-specific symptomatology - MG symptoms PRO[e]			
"Muscle weakness/fatigability" domain			
One-time improvement by ≥ 15 points on day 43	34 (51.5)	19 (28.4)	1.81 [1.18; 2.80][d]; 0.007
"Physical fatigue" domain			
One-time improvement by ≥ 15 points on day 43	31 (47.0)	26 (38.8)	1.19 [0.80; 1.77]; 0.395
"Bulbar muscle weakness" domain			
One-time improvement by ≥ 15 points on day 43	34 (51.5)	16 (23.9)	2.05 [1.26; 3.34]; 0.004
"Respiratory muscle weakness" domain			
One-time improvement by ≥ 15 points on day 43	25 (37.9)	17 (25.4)	Model does not converge[f]
"Ocular muscle weakness" domain			
One-time improvement by ≥ 15 points on day 43	20 (30.3)	11 (16.4)	2.17 [1.13; 4.14]; 0.019
General health status - EQ-5D-5L visual analogue scale[g]			
Improvement by ≥ 15 points on day 43	26 (39.4)	19 (28.4)	1.41 [0.90; 2.20][d] 0.138

Health-related quality of life

Endpoint	Rozanolixizumab n = 66	Placebo n = 67	Rozanolixizumab vs placebo
	Patients with event n (%)	Patients with event n (%)	RR [95% CI][a]; p value[b]
Myasthenia gravis quality of life 15-item scale score (MG-Qol15r-Score)[h]			
One-time improvement of MG-Qol15r score by ≥ 5 points on day 43	31 (47.0)	12 (17.9)	2.58 [1.46; 4.56]; 0.001

Side effects[i]

Endpoint **MedDRA system organ classes/ preferred terms/ AEs of special interest**	**Rozanolixizumab n = 64**	**Placebo n = 67**	**Rozanolixizumab vs placebo**
	Patients with event n (%)	*Patients with event n (%)*	RR [95% CI][j] p value[b]
Total adverse events (presented additionally)	52 (81.3)	45 (67.2)	n.a.
Serious adverse events (SAE)	3 (4.7)	3 (4.7)	1.05 [0.22; 5.00]; 0.954
Severe adverse events (CTCAE grade ≥ 3)	5 (7.8)	6 (9.0)	0.87 [0.28; 2.72]; 0.814
Therapy discontinuation due to adverse events	2 (3.1)	2 (3.1)	1.05 [0.15; 7.21]; 0.963
Severe adverse events according to MedDRA (with an incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)			
No serious AEs ≥ 5% occurred.			
SAEs according to MedDRA (with an incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)			
No SAEs ≥ 5% occurred.			
Adverse events of special interest (with statistically significant difference between the treatment arms)			
No AEs of special interest occurred.			

a. The logistic regression takes into account the "treatment" covariates and the baseline value of the considered endpoint as well as the stratification factors MuSK (+/-) and AChR (+/-).
b. The p value is based on the Wald test.
c. Adding up the individual items results in a total MG-ADL score of 0 to 24, with higher values implying a higher symptom burden.
d. Inclusion of the baseline value as a dichotomised variable (≤ median; > median)
e. A value between 0 and 100 can be reached. A higher value indicates more frequent and more severe symptomatology.
f. By including the baseline value, no parameter estimator could be derived independently of the scaling (dichotomous or continuous).
g. Higher values correspond to a better health status.
h. The total score can be between 0 and 30 points, with higher values indicating greater impairment of mental and social well-being.
i. The evaluation was carried out until the end of the observation (day 99, visit 14).
j. A logistic regression was performed with the "treatment" covariate.

Abbreviations used:

AChR: acetylcholine receptor; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D-VAS: Visual Analogue Scale of the European Quality of Life – 5 Dimensions; n.d.: no data available; CI: confidence interval; MG Symptoms PRO: Myasthenia Gravis Symptoms Patient Reported Outcome; MG-ADL: Myasthenia Gravis Activities of Daily Living; MG-QoL15r: Myasthenia Gravis Quality of Life 15-item Scale – Revised; MuSK: muscle-specific tyrosine kinase; RR: relative risk; (S)AE: (serious) adverse event; vs = versus.

b) Adults with anti-MuSK antibody-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↔	No relevant differences for the benefit assessment.
Health-related quality of life	↔	No relevant differences for the benefit assessment.
Side effects	↔	No relevant differences for the benefit assessment.
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		

MG0003 study: Phase III RCT, rozanolixizumab versus placebo, 1 treatment cycle (42 days) + 8 weeks follow-up, sub-population with anti-MuSK antibody-positive[2] generalised myasthenia gravis

Mortality

Endpoint	Rozanolixizumab n = 6	Placebo n = 7
	Patients with event n (%)	Patients with event n (%)
Mortality		
	No deaths have occurred.	

[2] ITT population of subjects with a positive anti-MuSK antibody status Population post IWRS randomisation.

Morbidity

Endpoint	Rozanolixizumab n = 6	Placebo n = 7	Rozanolixizumab vs placebo
	Patients with event n (%)	Patients with event n (%)	RR [95% CI][a]; p value[b]
Disease-specific symptomatology - Myasthenia Gravis (MG) Activities of Daily Living (ADL)[c]			
One-time improvement of the MG-ADL by ≥ 4 points on day 43	5 (83.1)	1 (14.3)	5.83 [0.92; 37.08] 0.061
Disease-specific symptomatology - MG symptoms PRO[d]			
"Muscle weakness/fatigability" domain			
One-time improvement by ≥ 15 points on day 43	4 (66.7)	1 (14.3)	4.67 [0.70; 31.22]; 0.112
"Physical fatigue" domain			
One-time improvement by ≥ 15 points on day 43	5 (83.3)	1 (14.3)	5.83 [0.92; 37.08]; 0.061
"Bulbar muscle weakness" domain			
One-time improvement by ≥ 15 points on day 43	4 (66.7)	1 (14.3)	4.67 [0.70; 31.22]; 0.112
"Respiratory muscle weakness" domain			
One-time improvement by ≥ 15 points on day 43	5 (83.3)	1 (14.3)	5.83 [0.92; 37.08]; 0.061
"Ocular muscle weakness" domain			
One-time improvement by ≥ 15 points on day 43	4 (66.7)	0	10.29 [0.66; 159.30]; 0.095

Health-related quality of life

Endpoint	Rozanolixizumab n = 6	Placebo n = 7	Rozanolixizumab vs placebo
	Patients with event n (%)	Patients with event n (%)	RR [95% CI][a]; p value[b]
Myasthenia gravis quality of life 15-item scale score (MG-Qol15r-Score)[j]			
One-time improvement of MG-Qol15r score by ≥ 5 points on day 43	5 (83.3)	1 (14.3)	5.83 [0.92; 37.08]; 0.061

Side effects[k]

Endpoint MedDRA system organ classes/ preferred terms/ AEs of special interest	Rozanolixizumab n = 5	Placebo n = 7	Rozanolixizumab vs placebo
	Patients with event n (%)	*Patients with event n (%)*	RR [95% CI][a] p value[l]
Total adverse events (presented additionally)	4 (80.0)	3 (42.9)	n.a.
Serious adverse events (SAE)	0	0	-
Severe adverse events (CTCAE grade ≥ 3)	0	0	-
Therapy discontinuation due to adverse events	0	0	-

a. The RR was calculated using non-parametric analyses (2x2 contingency tables) and zero cell correction.
b. The p values and the 95% CI were calculated under the normal distribution assumption.
c. Adding up the individual items results in a total MG-ADL score of 0 to 24, with higher values implying a higher symptom burden.
d. A value between 0 and 100 can be reached. A higher value indicates more frequent and more severe symptomatology.
e. Higher values correspond to a better health status.
f. A logistic regression was performed with the "treatment" covariate.
g. The analysis is based on the evaluation strategy ("hypothetical & treatment policy strategy") in which the administration of an emergency therapy leads to the subject with disease concerned being classified as absent in the evaluation. Based on the available documentation, it is assumed that this applied to 3 subjects from the placebo cohort and 1 subject from the intervention arm.
j. The total score can be between 0 and 30 points, with higher values indicating greater impairment of mental and social well-being.
k. The evaluation was carried out until the end of the observation (day 99, visit 14).
l. The p value is based on the Wald test.

Abbreviations used:

AChR: acetylcholine receptor; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D-VAS: Visual Analogue Scale of the European Quality of Life – 5 Dimensions; n.d.: no data available; CI: confidence interval; MG Symptoms PRO: Myasthenia Gravis Symptoms Patient Reported Outcome; MG-ADL: Myasthenia Gravis Activities of Daily Living; MG-QoL15r: Myasthenia Gravis Quality of Life 15-item Scale – Revised; MuSK: muscle-specific tyrosine kinase; n.a.: not assessable; RR: relative risk; (S)AE: (serious) adverse event; vs = versus.

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

a) Adults with anti-AChR antibody-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy

Approx. 6,300 - 19,000 patients

b) Adults with anti-MuSK antibody-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy

Approx. 170 – 300 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 Rystiggo (active ingredient: rozanolixizumab) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 23 May 2024):

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

Treatment with rozanolixizumab should only be initiated and monitored by doctors experienced in treating neuromuscular or neuroinflammatory diseases.

4. Treatment costs

Annual treatment costs:

a) Adults with anti-AChR antibody-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Rozanolixizumab	€ 318,235.07 - € 612,897.17
Patient-individual standard therapy	
Azathioprine	€ 323.65 - € 463.66
Prednisolone	€ 47.82 - € 103.67
Prednisone	€ 52.23 - € 119.57
Pyridostigmine	€ 215.93 - € 5,039.63
Neostigmine	Different from patient to patient
Distigmine	€ 1,477.52
Mycophenolate mofetil[3]	€ 549.56 - € 2,747.79

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 July 2024

Costs for additionally required SHI services: not applicable

[3] Mycophenolate mofetil is not approved in the therapeutic indication under consideration, but is reimbursable within the framework of off-label use (Pharmaceuticals Directive Annex VI) in the case of resistance to treatment with the approved substances or in the case of azathioprine intolerance.

b) Adults with anti-MuSK antibody-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Rozanolixizumab	€ 318,235.07 - € 612,897.17
Patient-individual standard therapy	
Azathioprine	€ 323.65 - € 463.66
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Mycophenolate mofetil[4]	€ 549.56 - € 2,747.79

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 July 2024

Costs for additionally required SHI services: not applicable

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) Adults with anti-AChR antibody-positive generalised myasthenia gravis who are eligible for an add-on to standard therapy

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.

[4] Mycophenolate mofetil is not approved in the therapeutic indication under consideration, but is reimbursable within the framework of off-label use (Pharmaceuticals Directive Annex VI) in the case of resistance to treatment with the approved substances or in the case of azathioprine intolerance.

b) Adults with anti-MuSK antibody-positive generalised myasthenia gravis who are eligible for an add-on to standard 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 15 August 2024.

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

Berlin, 15 August 2024

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

Prof. Hecken