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
Omaveloxolone (Friedreich's ataxia, ≥ 16 years)

of 19 September 2024

At its session on 19 September 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 Omaveloxolone as follows:

Omaveloxolone

Resolution of: 19 September 2024
Entry into force on: 19 September 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 9 February 2024):

Skyclarys is indicated for the treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older.

Therapeutic indication of the resolution (resolution of 19 September 2024):

See therapeutic indication according to marketing authorisation.

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

Omaveloxolone 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).

Adults and adolescents aged 16 years and older with Friedreich's ataxia

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

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

Study results according to endpoints:[1]

Adults and adolescents aged 16 years and older with Friedreich's ataxia

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		

MOXIe study (part 2):

- randomised, controlled, double-blind, phase II study
- Omaveloxolone vs placebo

Mortality

Endpoint	Omaveloxolone		Placebo		Omaveloxolone vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Overall mortality[a]					
No deaths occurred.					

[1] Data from the dossier assessment of the G-BA (published on 17. Juni 2024), and from the amendment to the dossier assessment from 7 August 2024, unless otherwise indicated.

Morbidity

Endpoint	Omaveloxolone			Placebo			Omaveloxolone vs placebo
	N[b]	Baseline MV (SD)	Change from baseline to week 48 LS mean (SE)	N[b]	Baseline MV (SD)	Change from baseline to week 48 LS mean (SE)	LS mean difference [95% CI]; p value *Hedges' g [95% CI]*
Physical functioning - modified Friedreich's Ataxia Rating Scale (93-point mFARS)[c]							
	51[d]	40.7 (10.2)	-1.01 (0.64)	52[d]	37.8 (10.8)	0.82 (0.60)	-1.82 [-3.59; -0.06]; 0.043 *-0.42 [-0.84; -0.01]*

Endpoint	Omaveloxolone		Placebo		Omaveloxolone vs placebo
	N[b]	Patients with event n (%)	N[b]	Patients with event n (%)	RR [95% CI]; p value
General health status - Patient Global Impression of Change (PGI-C)					
Improvement[f] at week 48	44	19 (43.2)	51	13 (25.5)	1.69 [0.95; 3.01]; 0.08
Deterioration[g] at week 48	44	13 (29.5)	51	23 (45.1)	0.66 [0.38; 1.14]; 0.13

Endpoint	Omaveloxolone			Placebo			Omaveloxolone vs placebo
	N[b]	Baseline MV (SD)	Change from baseline to week 48 LS mean (SE)	N[b]	Baseline MV (SD)	Change from baseline to week 48 LS mean (SE)	LS mean difference [95% CI]; p value
Activities of Daily Living (ADL)[h]							
	51[i]	11.0 (4.5)	0.28 (0.42)	52[i]	9.9 (4.7)	1.05 (0.39)	-0.78 [-1.93; 0.38]; 0.19

Health-related quality of life

Endpoint	Omaveloxolone		Placebo		Omaveloxolone vs placebo
	N[b]	Patients with event n (%)	N[b]	Patients with event n (%)	RR [95% CI]; p value
Short Form (36)-health survey (SF-36)					
Mental Component Summary (MCS) score[j]					
Deterioration[k] at week 48	44	3 (6.8)	51	3 (5.9)	1.16 [0.25; 5.42]; 0.85
Physical component summary (PCS) score[j]					
Deterioration[k] at week 48	44	3 (6.8)	51	4 (7.8)	0.89 [0.21; 3.71]; 0.87

Side effects

Endpoint	Omaveloxolone		Placebo		Omaveloxolone vs placebo
	N[l]	Patients with event n (%)	N[l]	Patients with event n (%)	RR [95% CI]; p value
Total adverse events *(presented additionally)*					
	51[m]	*51 (100)*	*52*[m]	*52 (100)*	-
Severe adverse events[n]					
	51[m]	5 (9.8)	52[m]	0 (0)	11.21 [0.64; 197.67]; 0.10
Serious adverse events (SAE)[o]					
	51[m]	5 (9.8)	52[m]	3 (5.8)	1.70 [0.43; 6.74]; 0.45
Therapy discontinuation due to adverse events					
	51[m]	4 (7.8)	52[m]	2 (3.8)	2.04 [0.39; 10.65]; 0.40
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)					
Severe AEs did not occur in any SOC and PT in ≥ 5% of subjects in any study arm.					
SAEs according to MedDRA (with an incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)					
In the SOC "cardiac disorders", SAEs occurred in 3 patients (5.9%) in the omaveloxolone arm and in 1 patient (1.9%) in the placebo arm. Effect estimators are not available.					

Adverse events of special interest (with statistically significant difference between the treatment arms)
No AEs of special interest were pre-specified.
a. Fatalities were recorded using safety. b. ITT population (includes all randomised patients) c. Scale from 0 to 93 points; higher values correspond to more serious physical impairments. d. Number of subjects at week 48: N = 42 in the omaveloxolone arm and N = 50 in the placebo arm. The number corresponds to those subjects who were included in the calculation of the change from baseline to week 48. e. Number of subjects at week 48: N = 34 in the omaveloxolone arm and N = 41 in the placebo arm. The number corresponds to those subjects who were included in the calculation of the change from baseline to week 48. f. Improvement is defined as < 4 points (any improvement) in the PGI-C. g. Deterioration is defined as > 4 points (any deterioration) in the PGI-C. h. Scale from 0 to 36 points; higher values correspond to strongly pronounced limitation in the activities of daily living. i. Number of subjects at week 48: N = 44 in the omaveloxolone arm and N = 51 in the placebo arm. The number corresponds to those subjects who were included in the calculation of the change from baseline to week 48. j. Higher values correspond to better quality of life. k. Deterioration was defined as a change from baseline to week 48 by ≤ -9.4 points in the PCS and ≤ -9.6 points in the MCS. This corresponds to 15 % of the scale range. l. Safety population (includes all patients who have received at least one dose of the randomised study medication) m. 6 subjects (11.8%) in the omaveloxolone arm and 1 subject (1.9%) in the placebo arm discontinued the study prematurely. n. Symptoms leading to incapacity to perform usual social and functional activities o. Fulfils one of the following criteria: Death, life-threatening, required hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or substantial impairment to perform normal life functions, congenital anomaly/ birth defect, major medical event
Abbreviations: ADL = Activities of Daily Living; ITT = Intention To Treat; CI = confidence interval; MCS = Mental Component Summary; MV = mean value; PCS = Physical Component Summary; PGI-C = Patient Global Impression of Change; RR = relative risk; SD = standard deviation; SE: standard error; SF-36 = Short-Form-36 Health Survey; (S)AE: (serious) adverse event.

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

Adults and adolescents aged 16 years and older with Friedreich's ataxia

Approx. 970 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 Skyclarys (active ingredient: omaveloxolone) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 01 August 2024):

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

Treatment with omaveloxolone should only be initiated and monitored by doctors experienced in treating patients with Friedreich's ataxia.

4. Treatment costs

Annual treatment costs:

Adults and adolescents aged 16 years and older with Friedreich's ataxia

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Omaveloxolone	€ 326,441.32

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

Adults and adolescents aged 16 years and older with Friedreich's ataxia

- 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.

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 19 September 2024.

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

Berlin, 19 September 2024

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

Prof. Hecken