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 Efgartigimod alfa (Myasthenia Gravis, AChR-antibody+)

of 16 February 2023

At its session on 16 February 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. **Annex XII shall be amended in alphabetical order to include the active ingredient Efgartigimod alfa as follows:**

Efgartigimod alfa

Resolution of: 16 February 2023
Entry into force on: 16 February 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 10 August 2022):

Vyvgart is indicated as an add-on to standard therapy for the treatment of adult patients with generalised Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive.

Therapeutic indication of the resolution (resolution of 16 February 2023):

See therapeutic indication according to marketing authorisation.

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

Efgartigimod alfa is approved as a medicinal product for the treatment of rare diseases under 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).

<u>Adults with generalised Myasthenia Gravis who are anti-acetylcholine receptor antibody positive</u>

Extent of the additional benefit and significance of the evidence of efgartigimod alfa as an add-on to standard therapy:

Hint for a considerable additional benefit

Study results according to endpoints:[1]

Adults with generalised Myasthenia Gravis who are anti-acetylcholine receptor antibody positive

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↑	Advantage in disease-specific symptomatology and general health status.
Health-related quality of life	↑	Advantage in MG-QoL15r.
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 ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

ADAPT study: RCT over up to 26 weeks; efgartigimod alfa vs placebo in each case as an add-on to standard therapy; AChR antibody-positive sub-population

Mortality

Endpoint	Efgartigimod alfa N = 65	Placebo N = 64
	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 1. Dezember 2022), unless otherwise indicated.

Morbidity

Endpoint	**Efgartigimod alfa** N = 65		**Placebo** N = 64		**Efgartigimod vs placebo**
	Baseline MV (SD)	Change LS-MV [SE] [95% CI]	Baseline MV (SD)	Change LS-MV [SE] [95% CI]	Difference LS-MD [95% CI]; p value
Disease-specific symptomatology - Myasthenia Gravis Activities of Daily Living (MG-ADL)					
Change in AUC MG-ADL over 20 weeks	9.0 (2.48)	-	8.6 (2.14)	-	-[a] < 0.001 Hedges' g [95% CI] - 0.68 [-1.035; -0.328]

Endpoint	**Efgartigimod alfa** N = 65		**placebo** N = 63[b]		**Efgartigimod vs placebo**
	N	Patients with event[c] n (%)	N	Patients with event[c] n (%)	RR [95% CI][d]; p value
Improvement in MG-ADL by ≥ 4 points from ≥ 4 consecutive weeks in treatment cycle 1	65	29 (44.6)	64	8 (12.5)	3.57 [1.77; 7.21]; < 0.001
Disease-specific symptomatology - Quantitative Myasthenia Gravis (QMG)					
One-time improvement of the QMG score by ≥ 6 points in treatment cycle 1	65	46 (70.8)	63	7 (11.1)	6.37 [3.11; 13.03]; < 0.001
General health status - EQ-5D-5L Visual Analogue Scale					
Improvement by ≥ 15 points in treatment cycle 1	65	44 (67.7)	63	21 (33.3)	2.03 [1.38; 2.99]; < 0.001

Health-related quality of life

Endpoint	Efgartigimod alfa		placebo		Efgartigimod vs placebo
	N	Patients with event[c] n (%)	N	Patients with event[c] n (%)	RR [95% CI][d]; p value
Myasthenia Gravis Quality of Life 15-item scale score					
One-time improvement of MG-Qol15r score by ≥ 5 points in treatment cycle 1	65	43 (66.2)	63	25 (39.7)	1.67 [1.17; 2.37]; 0.004

Side effects

Endpoint *MedDRA system organ classes;* Preferred terms	**Efgartigimod alfa N = 65**	**placebo N = 64**	**Efgartigimod vs placebo**
	Patients with event n (%)	Patients with event n (%)	RR [95% CI][c,e]; p value[e]
Adverse events in total[f]			
	49 (75.4)	54 (84.4)	-
Severe AEs (CTCAE grade ≥ 3)			
	6 (9.2)	7 (10.9)	0.84 [0.30; 2.374]; 0.778
Serious AE			
	3 (4.6)	6 (9.4)	0.49 [0.13; 1.88]; 0.324
Therapy discontinuation due to adverse events[g]			
	2 (3.1)	3 (4.7)	0.66 [0.11; 3.8]; 0.680
AE with an incidence of ≥ 10% in one of the study arms and a difference of ≥ 5% between the treatment groups			
General disorders and administration site conditions	5 (7.7)	10 (15.6)	0.49 [0.18; 1.36]; 0.181
Infections and infestations[h]	29 (44.6)	22 (34.4)	1.3 [0.84; 2.00]; 0.281
Upper respiratory tract infection[h]	9 (13.8)	2 (3.1)	4.43 [1.0; 19.71]; 0.054
Nervous system disorders	20 (30.8)	26 (40.6)	0.76 [0.47; 1.21];

			0.273

[a] Mean values depend on the observation period and are therefore not interpretable. Mean values are not interpretable.
[b] Does not correspond to the ITT population
[c] Corresponds to a one-time improvement by the respective points indicated. All subjects with an available value were taken into account. The pharmaceutical company does not provide any information on the imputation percentage of missing values.
[d] The stratification factors of randomisation were not considered in the analysis.
[e] Post hoc analysis
[f] The pharmaceutical company does not submit any additional evaluations that do not take disease-related events or events of the underlying disease into account. It can be assumed that events of the underlying disease were included in the recording of the AEs.
[g] Study participants received study medication until the need for emergency therapy, pregnancy, life-threatening SAE or an SAE that poses a serious safety risk, or initiation of an unauthorised medication as per the protocol, whichever occurred earlier.
[h] AEs of special interest

Abbreviations used:
AUC: Area Under the Curve; CTCAE = Common Terminology Criteria for Adverse Events; EQ5D- 5L-VAS = European Quality of Life 5-Dimension 5-Level Visual Analogue Scale; ITT= Intention-to-Treat; CI = confidence interval; LS-MV = Least-Square Mean Value; LS-MD = Least Square Mean Difference; MedDRA: Medical Dictionary for Regulatory Activities; MG-ADL: Myasthenia Gravis Activities of Daily Living; MV: mean value; N = number of patients evaluated; n = number of patients with event; PC: pharmaceutical company; RR: relative risk; SD: standard deviation; SE: standard error; AE: adverse event; vs = versus

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

Adults with generalised Myasthenia Gravis who are anti-acetylcholine receptor antibody positive

approx. 14,000 – 16,800 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 Vyvgart (active ingredient: efgartigimod alfa) at the following publicly accessible link (last access: 25 November 2022):

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

Treatment with efgartigimod alfa should only be initiated and monitored by doctors experienced in the therapy of neuromuscular diseases.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Efgartigimod alfa	€ 68,750.08 -€ 508,750.59
Patient-individual standard therapy[2]:	
Azathioprine	€ 323.43 - € 477.64
Prednisolone	€ 47.71 - € 103.44
Prednisone	€ 52.12 - € 119.32
Pyridostigmine bromide	€ 194.80 -€ 5,038.75
Neostigmine methylsulfate	Different from patient to patient
Distigmine bromide	€ 1,181.43
Mycophenolate mofetil[3]	€ 549.51 -€ 2,747.57

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2023)

Costs for additionally required SHI services: not applicable

2 As an alternative to azathioprine and mycophenolate mofetil, patients may be treated with other non-steroidal immunosuppressants such as methotrexate, cyclosporine and tacrolimus. These are not approved in the therapeutic indication and are therefore not included in the costs.

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

5. 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 Efgartigimod alfa

Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients that can be used in a combination therapy with efgartigimod alfa for the treatment of adult patients with generalised Myasthenia Gravis who are anti-acetylcholine receptor (AChR) antibody positive on the basis of the marketing authorisation under the Medicinal Products Act:

Adults with generalised Myasthenia Gravis who are anti-acetylcholine receptor antibody positive

- No active ingredient that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 16 February 2023.

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

Berlin, 16 February 2023

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

Prof. Hecken