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) Vamorolone (Duchenne muscular dystrophy, ≥ 4 years)

of 4 July 2024

At its session on 4 July 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 Vamorolone as follows:

Vamorolone

Resolution of: 4 July 2024
Entry into force on: 4 July 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 14 December 2023):

AGAMREE is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients aged 4 years and older.

Therapeutic indication of the resolution (resolution of 4 July 2024):

See therapeutic indication according to marketing authorisation.

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

Vamorolone 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).

Patients aged 4 years and older with Duchenne muscular dystrophy

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

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

Study results according to endpoints:[1]

[1] Data from the dossier assessment of the G-BA (published on 15. April 2024), and from the amendment to the dossier assessment from 17 June 2024, unless otherwise indicated.

Patients aged 4 years and older with Duchenne muscular dystrophy

Summary of results for relevant clinical endpoints

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

VB15-004 study: RCT; comparison of vamorolone (6.0 mg/kg/day) with prednisone (0.75 mg/kg/day), treatment phase 1 (week 24)

Mortality

Endpoint	Vamorolone		Prednisone		Vamorolone vs prednisone
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Effect estimator [95% CI] p value
Mortality	No deaths occurred.				

Morbidity

Endpoint	Vamorolone			Prednisone			Vamorolone vs prednisone
	N[1)]	Baseline MV (SD)	Change from baseline to week 24 LS mean (SE)[2)3)]	N[1)]	Baseline MV (SD)	Change from baseline to week 24 LS mean (SE)[2)3)]	LS mean difference [95% CI][2)3)]; p value[2)]
TTSTAND (s)	30	5.97 (1.99)[4)]	-0.89 (0.37)	31	4.92 (1.51)[4)]	-1.24 (0.35)	0.36 [-0.63, 1.34] 0.48
TTRW (s)	28[5)]	6.57 (1.48)	-0.79 (0.20)	31[5)]	5.51 (1.16)	-0.96 (0.19)	0.17 [-0.35, 0.69] 0.527
TTCLIMB (s)		n.d.	-1.15 (0.29)		n.d.	-1.23 (0.28)	0.08 [-0.71, 0.87] 0.843
6MWT[6)] (m)	30	312.5 (56.19)[7)]	24.1 (10.28)[7)]	31	343.3 (55.84)[7)]	43.3 (9.78)[7)]	-19.14 [-44.78; 6.51] 0.14

Health-related quality of life

No data available.

Side effects

Endpoint *MedDRA system organ classes;* Preferred terms	Vamorolone		Prednisone		Vamorolone vs prednisone
	N[8)]	Patients with event n (%)	N[8)]	Patients with event n (%)	RR [95% CI][9)]; p value[10)]
Total adverse events (presented additionally)	28	25 (89.3)	31	26 (83.9)	-
Serious adverse events (SAE)	28	0 (0.0)	31	0 (0.0)	-
Severe adverse events (CTCAE grade ≥ 3)	28	0 (0.0)	31	1 (3.2)	0.37 [0.02; 8.68] 0.54
Therapy discontinuation due to adverse events	28	0 (0.0)	31	1 (3.2)[4)]	0.37 [0.02; 8.68] 0.54
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 significant differences.					
SAEs according to MedDRA (with an incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)					

Endpoint *MedDRA system organ classes;* Preferred terms	Vamorolone		Prednisone		Vamorolone vs prednisone
	N[8)]	Patients with event n (%)	N[8)]	Patients with event n (%)	RR [95% CI][9)]; p value[10)]
No SAEs have occurred.					
Adverse events of special interest (with statistically significant difference between the treatment arms)					
No significant differences.					

Endpoint	Vamorolone			Prednisone			Vamorolone vs prednisone
	N	Baseline MV (SD)	Change from baseline to week 24 LS mean (SE)[2)11)]	N	Baseline MV (SD)	Change from baseline to week 24 LS mean (SE)[2)11)]	LS mean difference [95% CI][2)11)]; p value[2)11)]
Body height (z score)	28[1)]	-1.04 (1.05)	0.51 (0.11)	30[1)]	-0.44 (1.03)	0.40 (0.10)	0.22 [0.05, 0.39] 0.013
Body weight (z score)	27[8)]	-0.32 (1.02)	0.59 (0.08)	30[8)]	0.25 (0.91)	0.33 (0.08)	0.27 [0.05, 0.48] 0.018

[1)] ITT population: All randomised patients.
[2)] Calculation of the LS mean and LSM difference using a REML-based MMRM. The treatment groups (vamorolone 2.0 mg/kg/day, vamorolone 6.0 mg/kg/day, prednisone 0.75 mg/kg/day or placebo), visits (weeks 6, 12 and 24), the interaction term treatment × visit, endpoint at baseline and age at baseline (< 6 years; ≥ 6 years) were included as independent variables. An unstructured covariance matrix was used.
[3)] The evaluation is based on imputed data (multiple imputation).
[4)] Information refer to the imputed values at week 24; deviating values from baseline (intervention: n = 28 (93.3%); control: n = 31 (100%)).
[5)] Data could only be identified for the mITT population (vamorolone 6.0 mg/kg/day) (N = 28) and prednisone 0.75 mg/kg/day (N = 31). 2 patients (6.7%) in the intervention group "vamorolone 6.0 mg/kg/day" and one patient (3.2%) in the control group "prednisone 0.75 mg/kg/day" withdrew prematurely from the study by week 24. For the remaining 3 subjects (9.3%) in the intervention arm "vamorolone 6.0 mg/kg/day" and 2 subjects (6.4%) in the control arm "prednisone 0.75 mg/kg/day", no information on the missing values could be identified.
[6)] The endpoints were collected from patients who completed the TTRW ≤ 25 s.
[7)] Information refers to the values at week 24 (after multiple imputation); deviating values from baseline (intervention: n = 26 (86.7%); control: n = 31 (100%)) and week 24 (intervention: n = 21 (70.0%); control: n = 22 (71.0%)).
[8)] Safety population: all randomised patients who received at least one dose of the study medication. The number corresponds to those patients who were used to calculate the respective statistics.
[9)] The relative risk [95% CI] and the p value were calculated post hoc for the dossier. According to dossier module 4, the relative risk was calculated using bidirectional table comparisons. In the case of 0 events in one treatment arm, a correction of 0.5 was made for all treatment groups. There is no data available on the statistical analytical procedure or whether adjustment by the age stratification characteristic was planned.
[10)] Calculated post hoc. For the efficacy endpoints, the calculation was done using the Fischer Exact test. It is unclear whether this was also applied to the safety endpoints.
[11)] The evaluation is based on the observed values.

Abbreviations:

6MWT: 6-Minute Walk Test; CTCAE: Common Terminology Criteria for Adverse Events; n.d.: no data available; CI: confidence interval; LSM: Least Square Means; MMRM: Mixed Model for Repeated Measures; MV: mean value; N = number of patients evaluated; n = number of patients with (at least one) event; REML: Restricted Maximum Likelihood; SD: standard deviation; SE: standard error; SAE: serious adverse event; TTCLIMB: time-to-climb test; TTRW: time-to-run/walk test; TTSTAND: time-to-stand test; AE: adverse event; vs = versus

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

Patients aged 4 years and older with Duchenne muscular dystrophy

Approx. 740 to 3,670 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 Agamree (active ingredient: vamorolone) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 9 February 2024):

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

Treatment with vamorolone should only be initiated and monitored by doctors experienced in treating Duchenne muscular dystrophy.

4. Treatment costs

Annual treatment costs:

Patients aged 4 years and older with Duchenne muscular dystrophy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Vamorolone	€ 21,063.45 - € 140,423.02

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

Patients aged 4 years and older with Duchenne muscular dystrophy

- 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.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 4 July 2024.

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

Berlin, 4 July 2024

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

Prof. Hecken