Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive (AM-RL)

Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V: Afamelanotide (Reassessment after the deadline: Phototoxicity in erythropoietic protoporphyria (EPP))

of 1 July 2021

At its session on 1 July 2021, 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 on DD. Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII is amended as follows:

1. The information on afamelanotide in the version of the resolution of 4 August 2016 (BAnz AT 22.9.2016 B2) is repealed.

2. Annex XII shall be amended in alphabetical order to include the active ingredient afamelanotide as follows:

Afamelanotide

Resolution of: 1 July 2021
Entry into force on: 1 July 2021
BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 22 December 2014):

Scenesse is indicated for prevention of phototoxicity in adult patients with erythropoietic protoporphyria (EPP).

Therapeutic indication of the resolution (resolution of 1 July 2021):

see therapeutic indication according to marketing authorisation

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

Afamelanotide 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 German Social Code, Book Five (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 Ordinance on the Benefit Assessment of Pharmaceuticals (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).

Adult patients with erythropoietic protoporphyria for the prevention of phototoxicity

Extend of the additional benefit and significance of the evidence of afamelanotide:

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

Study results according to endpoints:[1]

Adult patients with erythropoietic protoporphyria for the prevention of phototoxicity

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	There were no deaths.
Morbidity	↑	Advantage in duration of direct sunlight exposure on days without pain.
Health-related quality of life	↔	No relevant difference for the benefit assessment.
Side effects	n.a.	The data are not assessable.
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		

CUV039: Phase III study, RCT, comparison of afamelanotide vs placebo

CUV-PASS-001/002 (post-authorisation safety study): non-interventional study based on a disease registry, data cut-off from the 4th. interim report.

Mortality

Studies: CUV039, CUV-PASS-001/002 Endpoint	Afamelanotide	Placebo	Afamelanotide vs placebo
Overall survival			
There were no deaths.			

[1] Data from the dossier evaluation of the G-BA (published on the 1.4.2021), unless otherwise indicated.

Morbidity

Study: CUV039 Endpoint	Afamelanotide		Placebo		Afamelanotide vs placebo
	N	MV (SD) Median (min; max)	N	MV (SD) Median (min; max)	Effect estimator[g)] [95% CI] p value
Duration of direct sunlight exposure between 10:00 and 18:00 on days without pain[a)]					
Patient-individual total time[b)] (hours)	46	115.6 (140.6) 69.4 [0; 650.5]	43	60.6 (60.6) 40.8 [0; 224.0]	24.0 [0.3; 50.3] 0.044
Average[c)] Time (minutes/day)	46	43.3 (52.0) 25.9 [0; 260.2]	43	23.7 (22.5) 18.1 [0; 83.5]	8.8 [-0.8; 18.5] 0.075
Duration of direct sunlight exposure between 10:00 and 18:00 on days without pain or with low pain [d)]					
Patient-individual total time[b)] (hours)	46	141.1 (165.1) 80.0 [0.5; 825.0]	43	74.6 (67.5) 51.0 [1.25; 251.0]	26.8 [–0.3; 57.5] 0.053
Average[c)] Time (minutes/day)	46	47.5 (53.4) 27.3 [0.2; 263.3]	43	27.1 (22.9) 25.2 [0.7; 85.0]	8.4 [–1.5; 18.9] 0.094
Duration of direct sunlight exposure between 10:00 and 15:00 on days without pain[a)]					
Patient-individual total time[b)] (hours)	46	71.2 (89.2) 39.6 [0; 419.0]	43	41.6 (45.3) 31.8 [0; 198.8]	13.1 [–1.3; 28.0] 0.092
Average[c)] Time (minutes/day)	46	26.9 (33.3) 14.9 [0; 167.6]	43	16.4 (17.3) 11.0 [0; 74.1]	4.9 [–1.0; 10.6] 0.134
Total patient-individual phototoxicity during the study period: Pain in phototoxic episodes[e)]					
Total pain intensity (sum)	46	16.3 (33.2) 4.0 [0; 196]	43	34.1 (86.7) 6.0 [0; 507]	n. d. 0.442
Total maximum pain intensity	46	3.5 (3.1) 4.0 [0; 8]	43	3.9 (3.3) 5.0 [0; 9]	n. d. 0.544
Phototoxic episodes during the study period[f)]					
Number of episodes	46	2.0 (3.3) 1.0 [0; 15]	43	3.3 (6.8) 1.0 [0; 35]	n.d. 0.602
Number of days in the longest episode	46	1.3 (1.9) 1.0 [0; 12]	43	1.7 (2.1) 1.0 [0; 10]	n.d. 0.519
Total patient-individual phototoxicity during the study period: Number of days	46	3.2 (6.0) 1.0 [0; 34]	43	6.6 (16.8) 1.0 [0; 98]	n.d. 0.503

a) "Without pain" corresponds to a Likert value of 0 of the self-recording in the patient diary (scale range: 0–10).
b) The above (cumulative) times refer to the total time during the treatment phase.

Study: CUV039 Endpoint	Afamelanotide		Placebo		Afamelanotide vs placebo
	N	MV (SD) Median (min; max)	N	MV (SD) Median (min; max)	Effect estimator[g)] [95% CI] p value

c) The average number of minutes/day for each subject was calculated as the quotient of completely pain-free time with direct sunlight exposure and the number of all days with patient diary recording.
d) "With no pain or little pain" refers to the subject's self-recording in the patient diary in the pain scale with the Likert scale score range of 0 to 3 (scale range: 0–10).
e) Calculated by summing the scale values of the 11-point Likert scale (value range 0-10). Presentation of values only for all test subjects - regardless of whether at least one phototoxic episode occurred during the study.
f) A "phototoxic episode" is defined as a period of time (including periods of more than one day) in which the values on the patient diary pain scale were consistently above the value 3. The group differences for the subsample including only subjects with at least one phototoxic episode during the study were also all statistically insignificant.
g) Effect estimator according to Hodges-Lehmann, p-value based on Kruskal-Wallis. Analyses that took into account adjustment for stratification variable treatment centre" "were not presented.

Abbreviations: ITT: Intention-to-Treat; n. d.: no data; CI: Confidence interval; MV: Mean value; SD: Standard deviation

Health-related quality of life

Study: CUV039 Endpoint	Afamelanotide		Placebo		Afamelanotide vs placebo
	N	MV (SD) Median (min; max)	N	MV (SD) Median (min; max)	Effect estimator[a)] [95% CI] p value
Change in DLQI total score[b)] compared to baseline					
At day 60	47	-6 (5.9) -6.0 [-24; 2]	43	-4 (5.5) -5.0 [-15; 11]	–1 [–4; 1] 0.214
At day 120	46	-7.8 (6.0) -7.0 [-26; 0]	42	-6.5 (6.2) -6.5 [-17; 14]	–1 [-3; 2] 0.589
At day 180 or in case of early termination	46	-8.1 (6.2) -7.5 [-26; 1]	43	-7.3 (5.6) -8.0 [-19; 5]	0 [–3; 2] 0.799

a) Effect estimator according to Hodges-Lehmann, p-value based on Kruskal-Wallis. Analyses that took into account adjustment for stratification variable treatment centre" "were not presented.
b) The range of values is between 0 and 30, where 30 means maximum impairment.

Abbreviations: DLQI: Dermatology Life Quality Index; ITT: Intention-to-Treat; n. d.: no data; CI: Confidence interval; MV: Mean value; QoL: Quality of Life; SD: Standard deviation

Side effects

Study: CUV039 Endpoint	Afamelanotide		Placebo		Afamelanotide vs placebo
	N	Persons with event n (%)	N	Persons with event n (%)	RR [95%- CI] p value
Adverse events in total					
AE	48	45 (94)	45	39 (87)	-
Severe AE[a)]	48	10 (21)	45	7 (16)	n.d.
SAE	48	3 (6)	45	2 (4)	n.d.
AE, which led to the discontinuation of the study medication	48	0	45	0	-
Adverse events with incidence ≥ 10% in at least one treatment arm **SOC** - **PT**					
Gastrointestinal disorders	48	12 (25)	45	14 (31)	n.d.
- Nausea	48	9 (19)	45	8 (18)	n.d.
General disorders and administration site conditions	48	19 (40)	45	7 (16)	n.d.
- Discolorations at implant site	48	9 (19)	45	0	n.d.
Infections and infestations	48	15 (31)	45	22 (49)	n.d.
- Flu	48	2 (4)	45	7 (16)	n.d.
- Nasopharyngitis	48	6 (13)	45	10 (22)	n.d.
Musculoskeletal and connective tissue disorders	48	13 (27)	45	8 (18)	n.d.
- Arthralgia	48	5 (10)	45	2 (4)	n.d.
- Back pain	48	6 (13)	45	6 (13)	n.d.
Nervous system disorders	48	21 (44)	45	18 (40)	n.d.
- Headaches	48	19 (40)	45	13 (29)	n.d.
Eye disorders	48	5 (10)	45	1 (2)	n.d.
Respiratory, thoracic and mediastinal disorders	48	7 (15)	45	6 (13)	n.d.

Study: CUV039 Endpoint	Afamelanotide		Placebo		Afamelanotide vs placebo
	N	Persons with event n (%)	N	Persons with event n (%)	RR [95%- CI] p value
Severe adverse events with incidence ≥ 5% in at least one treatment arm **SOC** - **PT**					
Musculoskeletal and connective tissue disorders	48	4 (8)	45	2 (4)	n.d.
Nervous system disorders	48	4 (8)	45	2 (4)	n.d.
- Headaches	48	3 (6)	45	1 (2)	n.d.

a) Severe AEs are defined as significant impairment of the person's activities of daily living, and can be life-threatening.

Abbreviations: n. d.: no data; MedDRA Medical Dictionary for Regulatory Activities; PT: Preferred term according to MedDRA; AE: Adverse event; RR: Relative risk; (S)AE: (Serious) adverse event: SOC: System Organ Class according to MedDRA;

Study: PASS Endpoint	Afamelanotide	
	N	Persons with event n (%)
Adverse events in total		
AE	297	219 (73.7)
Severe AE[a)]	297	18 (6.1)
SAE	297	27 (9.1)
AE, which led to the discontinuation of the study medication	297	3 (1.0)
Adverse events with an incidence of ≥ 10% **SOC** - **PT**		
Gastrointestinal disorders	297	98 (33.0)
- Nausea	297	70 (23.6)
General disorders and administration site conditions	297	112 (37.7)
- Fatigue	297	43 (14.5)
Infections and infestations	297	69 (23.2)

Study: PASS Endpoint	Afamelanotide	
	N	Persons with event n (%)
Musculoskeletal and connective tissue disorders	297	36 (12.1)
Nervous system disorders	297	88 (29.6)
- Headaches	297	61 (20.5)
Skin and subcutaneous tissue disorders	297	68 (22.9)
Vascular disorders	297	37 (12.5)

a) Severe AEs are defined as significant impairment of the person's activities of daily living, and can be life-threatening.

Abbreviations: n. d.: no data; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred term according to MedDRA; AE: Adverse event; RR: Relative risk; (S)AE: (Serious) adverse event: SOC: System Organ Class according to MedDRA;

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

Adult patients with erythropoietic protoporphyria for the prevention of phototoxicity

approx. 540 to 1,090 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 Scenesse (active ingredient: afamelanotide) at the following publicly accessible link (last access: 16 April 2021):
https://www.ema.europa.eu/en/documents/product-information/scenesse-epar-product-information_de.pdf

Afamelanotide should only be prescribed by specialised physicians in recognised porphyria centres and only implanted by a doctor who has been trained and accredited by the marketing authorisation holder in the application of the implant.

As a risk minimisation measure, all medical professionals likely to use the product will be trained by the marketing authorisation holder. The following prescribed information material shall be made available: Summary of the characteristics of the medicinal product, face-to-face training material, information video and a register information sheet.

This medicinal product was approved under ”exceptional circumstances”. This means that due to the rarity of the disease, it was not possible to obtain complete information on this medicinal product. The European Medicines Agency will assess any new information that

becomes available on an annual basis, and, if necessary, the summary of product characteristics will be updated.

Depending on the duration of protection required, three implants per year are recommended. A maximum of four implants per year is recommended. The total duration of treatment is at the discretion of the specialist doctor.

4. Treatment costs

Annual treatment costs:

Adult patients with erythropoietic protoporphyria for the prevention of phototoxicity

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Afamelanotide	€ 51,875.85 - € 69 167,80

Costs after deduction of statutory rebates (LAUER-TAXE®, as last revised: 15 June 2021)

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the internet on the G-BA website on 1 July 2021.

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

Berlin, 1 July 2021

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken