Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) 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 Lanadelumab

of 1 August 2019

At its session on 1 August 2019, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive, AM-RL) in the version dated 18 December 2008/22 January 2009 (Federal Gazette, BAnz. no. 49a of 31 March 2009), last changed on DD Month YYY (BAnz AT DD MM YYY BX), to be amended as follows:

Resolution has been repealed

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

Courtesy translation – only the German version is legally binding.

Lanadelumab

Resolution of: 1 August 2019
Entry into force on: 1 August 2019
BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 22 November 2018):

Takhzyro is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 12 years and older.Extent of the additional benefit of the medicinal product

Lanadelumab 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. According to 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) 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).

Resolution has been repeated

Patients aged 12 years and older with recurrent attacks of hereditary angiooedema (HAE)

Extent of the additional benefit:

considerable

Study results according to endpoints:[1]

[1] Data from the dossier evaluation of the G-BA (published on 2 May 2019) and the amendment of 20 June 2019

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HELP study: Lanadelumab vs placebo

Mortality

Endpoint	Lanadelumab		Placebo	Lanadelumab vs Placebo	
	300 mg every 2 weeks	300 mg every 4 weeks		300 mg every 2 weeks	300 mg every 4 weeks
Mortality					
There have been no deaths.					

Morbidity

Endpoint	Lanadelumab				Placebo		Lanadelumab vs Placebo	
	300 mg every 2 weeks		300 mg every 4 weeks				300 mg every 2 weeks	300 mg every 4 weeks
	N	MV (SD)	N	MV (SD)	N	MV (SD)	Rate ratio (vs placebo) [95% CI] p value[1]	
Number of confirmed HAE attacks during the treatment phase (Day 0 to Day 182)								
Attack rate (attacks/ month)[2]	27	0.3 (0.5)	29	0.6 (0.8)	41	2.5 (2.1)	0.1 [0.1 to 0.2] < 0.001	0.3 [0.2 to 0.4] < 0.001
Number of confirmed moderate to severe HAE attacks during the treatment phase (Day 0 to Day 182)								
Attack rate (attacks/ month)[2]	27	0.2 (0.5)	29	0.4 (0.6)	41	1.4 (1.3)	0.2 [0.1 to 0.3] < 0.001	0.3 [0.2 to 0.5] < 0.001
Number of confirmed laryngeal attacks during the treatment phase (Day 0 to Day 182)								
Attack rate (attacks/ month)[2]	27	0.1 (0.2)	29	0.0 (0.0)	41	0.1 (0.4)	0.4 [0.1 to 2.3] 0.304	0.2 [0.0 to 1.8] 0.149
Number of confirmed HAE attacks leading to emergency or hospital admission during the treatment phase (Day 0 to Day 182)[3]								
Attack rate (attacks/ month)[2]	27	0.0 (0.2)	29	0.0 (0.1)	41	0.0 (0.1)	0.4 [0.0 to 3.3] 0.360	0.8 [0.2 to 4.1] 0.819

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Endpoint	Lanadelumab				Placebo		Lanadelumab vs Placebo	
	300 mg every 2 weeks		300 mg every 4 weeks				300 mg every 2 weeks	300 mg every 4 weeks
	N	days [95% CI]	N	days [95% CI]	N	days [95% CI]	Hazard Ratio[4] [95% CI][5] p value[6]	
Time to the first confirmed HAE attack (Day 0 to Day 182)								
Median observation time	27	no data available	29	no data available	41	no data available	0,3	0,4
Median time to the first attack (days) Median (95% CI)	27	59 [28 to n.c.]	29	28 [10 to 101]	41	8 [6 to 18]	[0.1 to 0.5] < 0.001	[0.2 to 0.7] < 0.001

Endpoint	Lanadelumab				Placebo		Lanadelumab vs Placebo	
	300 mg every 2 weeks		300 mg every 4 weeks				300 mg every 2 weeks	300 mg every 4 weeks
	N	n (%)	N	n (%)	N	n (%)	Relative risk (vs placebo) [95% CI] p value	
Achievement of confirmed absence of HAE attacks during the treatment phase (Day 0 to Day 182)								
Absence of attacks[8]	27	12 (44.4)	29	9 (31.0)	41	1 (2.4)	18.2 [2.5 to 132.2] < 0.001[7]	12.7 [1.7 to 95.0] 0.001[7]
EQ-5D-VAS: Responder analysis (MCID = 7.5)								
Responder	26	9 (34,6)	27	8 (29.6)	38	13 (34.2)	1.0 [0.5 to 2.0][9] 0.9733[10]	0.9 [0.4 to 1.8][9] 0.6971[10]
EQ-5D-VAS: Responder analysis (MCID = 10)								
Responder	26	9 (34,6)	27	8 (29.6)	38	13 (34.2)	1.0 [0.5 to 2.0][9] 0.9733[10]	0.9 [0.4 to 1.8][9] 0.6971[10]

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Endpoint	Lanadelumab				Placebo		Lanadelumab vs Placebo	
	300 mg every 2 weeks		300 mg every 4 weeks				300 mg every 2 weeks	300 mg every 4 weeks
	N	MV (SD)	N	MV (SD)	N	MV (SD)	Mean difference[11] vs placebo (ANCOVA[12]) [95% CI] p value[12.13]	
EQ-5D-VAS: Change from Day 0 to Day 182								
Change between Day 0 and Day 182[14]	26	2.1 (13.8)	27	−0.3 (20.0)	38	2.1 (18.1)	−0.6 [−10.8 to 9.7] > 0.05	−1.9 [−12.0 to 8.3] > 0.05

1. Adjusted p values are adjusted for multiple testing/unadjusted p-values are derived from the Poisson model (exploratory efficacy endpoints): laryngeal attacks and HAE attacks with emergency room stay)
2. A month is defined as a period of four weeks or 28 days.
3. The results of the number of confirmed HAE attacks leading to emergency room or hospital admission during the treatment phase (Day 0 to Day 182) are identical to stays in emergency rooms. Hospital stays in connection with HAE attacks did not take place in the study.
4. The HR and p values come from a proportional Cox model with the following covariates: Attack rate of the admission phase and treatment group.
5. The Wald test is used for confidence intervals and p values.
6. Based on a Log Rank test
7. Calculated with exact Fisher test
8. When the study was discontinued, “no absence of attacks” was imputed at this time.
9. Missing values were not taken into account.
10. Own calculations with OpenEpi, Chi square test
11. LS Mean Difference
12. ANCOVA model adjusted for baseline, pairwise T-test with Tukey Kramer approximation
13. p value not further limited
14. If no end-of-treatment data were available, the last available time was used to calculate the change from baseline. However, the time had to have been determined at least 9 weeks after baseline. If this value was not available, the change from baseline was not calculated.

Abbreviations: ANCOVA. Analysis of covariance; EQ-5D: EuroQoL Group 5 Dimension Questionnaire; HAE: Hereditary angiooedema; HR: Hazard ratio; CI: Confidence interval; LS: Least Squares; MCID: Minimal clinically important difference; MW: Mean Value; N: Number of patients evaluated; n: Number of patients with (at least one) event; SD: Standard deviation; VAS: visual analogue scale; vs: versus

Resolution has been reported

Health-related quality of life

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Endpoint	Lanadelumab				Placebo		Lanadelumab vs Placebo	
	300 mg every 2 weeks		300 mg every 4 weeks				300 mg every 2 weeks	300 mg every 4 weeks
	N	n (%)	N	n (%)	N	n (%)	Relative risk (vs placebo)[1] [95% CI] p value[2]	
AE-QoL total: Responder analysis (MCID = 6)								
Responder	26	21 (80.8)	27	17 (63.0)	38	14 (36.8)	2.2 [1.4 to 3.5] 0.0008	1.7 [1.0 to 2.8] 0.0383

Endpoint	Lanadelumab				Placebo		Lanadelumab vs Placebo	
	300 mg every 2 weeks		300 mg every 4 weeks				300 mg every 2 weeks	300 mg every 4 weeks
	N	MV (SD)	N	MV (SD)	N	MV (SD)	Mean difference[3] vs placebo (ANCOVA[4]) [95% CI] p value	
AE-QoL: Change from Day 0 to Day 182								
AE-QoL total	26	−20.9 (19.9)	27	−18.0 (21.5)	38	−3.8 (14.5)	−16.6 [−28.5 to −4.6] 0.00253[1.4] *Hedges' g* [95% CI]: −0.9 [−1.4 to −0.4]	−12.7 [−24.5 to −0.8] 0.0315[1.4] *Hedges' g* [95% CI]: −0.7 [−1.2 to −0.18]
AE-QoL function	26	−35.4 (24.8)	27	−24.3 (32.1)	38	−4.7 (23.3)	−30.6 [−45.1 to −16.0] < 0.0001[2.4] *Hedges' g* [95% CI]: −1.3 [−1.9 to −0.8]	−18.9 [−33.2 to −4.5] 0.0046[2.4] *Hedges' g* [95% CI]: −0.8 [−1.3 to −0.3]
AE-QoL fatigue/mood	26	−15.4 (28.9)	27	−15.0 (22.6)	38	−1.1 (21.5)	−14.0 [−28.8 to 0.9] 0.0721[2.4]	−12.1 [−26.8 to 2.7] 0.1474[2.4]

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AE-QoL anxiety/shame	26	−17.5 (29.1)	27	−17.3 (27.5)	38	−6.4 (16.4)	−8.6 [23.8 to 6.6] 0.4582[2.4]	−7.3 [−22.4 to 7.8] 0.5919[2.4]
AE-QoL nutrition	26	−15.9 (20.5)	27	−13.0 (32.6)	38	−2.0 (18.5)	−18.5 [−33.0 to −4.1] 0.0059[2.4] *Hedges' g* [95% CI]: −0.8 [−1.3 to −0.3]	−13.8 [−28.0; 0.34] 0.0584[2.4] *Hedges' g* [95% CI]: -

1. Missing values were not taken into account. Calculated post hoc by the pharmaceutical company. No information on the test used. In accordance with recalculations, a Chi square test appears to have been used.
2. p value is only available in manufacturer dossier M4 and post-evaluations submitted.
3. LS Mean Difference
4. ANCOVA model adjusted for the baseline value of the corresponding domain; pairwise t-test with Tukey Kramer approximation

Abbreviations: AE-QoL: Angiooedema Quality of Life Questionnaire; ANCOVA. Analysis of Covariance; CI: Confidence interval; LS: Least Squares; MCID: Minimal clinically important difference; N: Number of patients evaluated; n: Number of patients with (at least one) event; vs: versus

n repealed

Side effects

Endpoint	**Lanadelumab**				**Placebo**		**Lanadelumab vs Placebo**	
	300 mg every 2 weeks		300 mg every 4 weeks				300 mg every 2 weeks	300 mg every 4 weeks
	N	n (%)	N	n (%)	N	MV (SD)	Relative risk [95% CI] p value	
AE	27	26 (96.3)	29	25 (86.2)	41	31 (75.6)	no data available[1]	no data available[1]
Severe AE	27	2 (7.4)	29	4 (13.8)	41	4 (9.8)		
SAE	27	1 (3.7)	29	3 (10.3)	41	0	4.5[2] [0.2 to 106.6] 0.397[3]	9.8[2] [0.5 to 182.8] 0.067[3]
AE that led to discontinuation of the trial drug	27	0	29	1 (3.4)	41	1 (2.4)	0.5[4] [0.0 to 11.8] 1.000[3]	1.4[4] [0.1 to 21.7] 1.000[3]
AE leading to death	27	0	29	0	41	0		
AE of special interest	27	3 (11.1)	29	1 (3.4)	41	0	10.5[2] [0.6 to 195.5] 0.058[3]	4.2[2] [0.2 to 99.6] 0.414[3]

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1. There is no effect estimator available for this comparison. A priori, no comparative statistics were planned for severe AE. Module 4 of the manufacturer dossier summarises the moderate and severe AE categories.
2. Recalculated post hoc for the module of the manufacturer dossier. Primarily planned analyses were relative risks, risk differences in each case compared with placebo with correspondingly exact 95% CI for serious adverse events, and AE of special interest. Both analyses were reported as non-estimated in the study report.
3. Calculated with exact Fisher test.
4. Calculated post hoc for the module of the manufacturer dossier. Recalculated post hoc for the module of the manufacturer dossier. Primarily planned analyses were relative

Abbreviations: MV: mean; MedDRA: Medical Dictionary for Regulatory Activities; N: Number of patients evaluated; n: Number of patients with (at least one) event; PT: Preferred Term; SD: Standard deviation; SOC: System Organ Class; SAE: Serious adverse event
AE: adverse event; vs: versus

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

Approx. 140–430 patients

2. 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 Takhzyro® (active ingredient: lanadelumab) at the following publicly accessible link (last access: 28 May 2019):

https://www.ema.europa.eu/documents/product-information/takhzyro-epar-product-information_de.pdf

Lanadelumab treatment should be initiated and monitored by physicians with experience in treating patients with hereditary angiooedema (HAE).

Resolution has been repealed

3. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Lanadelumab	€ 212,951.77–425,903.53

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 July 2019)

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 website of the G-BA on 1 August 2019.

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

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Berlin, 1 August 2019

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

Prof Hecken

Resolution has been repealed

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