Resolution

Gemeinsamer Bundesausschuss

of the Resolution 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 Amikacin (Mycobacterium avium complex pulmonary infections)

of 20 May 2021

At its meeting on 20 May 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 shall be amended in alphabetical order to include the active ingredient amikacin as follows:

Amikacin

Resolution of: 20 May 2021
Entry into force on: 20 May 2021
BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 27 October 2020):

Arikayce liposomal is indicated for the treatment of non-tuberculous mycobacterial (NTM) lung infections caused by *Mycobacterium avium* Complex (MAC) in adults with limited treatment options, who do not have cystic fibrosis.

Therapeutic indication of the resolution (resolution of 20/05/2021):

see therapeutic indication according to marketing authorisation.

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

Amikacin (liposomal formulation) 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).

Treatment of non-tuberculous mycobacterial (NTM) pulmonary infections caused by *Mycobacterium avium* Complex (MAC) in adults with limited treatment options, who do not have cystic fibrosis

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

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

Study results according to endpoints:[1]

Treatment of non-tuberculous mycobacterial (NTM) pulmonary infections caused by *Mycobacterium avium* Complex (MAC) in adults with limited treatment options, who do not have cystic fibrosis

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment.
Morbidity	↔	No relevant difference for the benefit assessment.
Health-related quality of life	n.a.	The data are not assessable.
Side effects	↓	Disadvantages in severe AEs and in AEs that led to discontinuation of study medication.
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 is no usable data for the benefit assessment. n.a.: not assessable		

CONVERT study: Amikacin liposomal (ALIS) + antibiotic combination therapy (MDR) vs antibiotic combination therapy (MDR). Treatment phase 16 months, follow-up 12 months.

Mortality

Endpoint	ALIS + MDR		MDR		ALIS + MDR vs MDR
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value
Overall survival					
Deaths (up to month 8)	224	3 (1.3)	112	3 (2.7)	no data
Abbreviations: ALIS: liposomal amikacin for inhalation; n.d.: no data; CI: Confidence interval; MDR: Multi-drug regimens (antibiotic combination therapy)					

Morbidity

[1] Data from the dossier assessment of the G-BA (published on 1 March 2021), and from the amendment to the dossier assessment, unless otherwise indicated.

Endpoint	ALIS + MDR		MDR		ALIS + MDR vs MDR
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95%- CI] p value
Pathogen-free (presented additionally)					
Sputum conversion up to month 6 [a)]	224	65 (29.0)	112	10 (8.9)	3.28 [1.76; 6.10] < 0.0001
Pathogen-free 12 months under treatment after cultural sputum conversion [b)]	224	41 (18.3)	112	3 (2.7)	6.90 [2.20; 21.60] < 0.0001
Pathogen-free 3 months after cessation of therapy for 12 months after cultural sputum conversion [b)]	224	36 (16.1)	112	0	n. d. < 0.0001
Pathogen-free 12 months after cessation of therapy for 12 months after cultural sputum conversion [b)]	224	30 (13.4)	112	0	n. d. < 0.0001

a) Patients with at least 3 MAC-negative sputum cultures collected in consecutive months up to month 6 were considered converters.
b) Only patients with 12 months of treatment within the CONVERT study were considered pathogen-free. Converters were still considered pathogen-free if they had no more than 2 consecutive positive liquid cultures and no agar-positive solid culture by the time of analysis. In case of death, absence of sputum sample or absence of visit, the respective person was scored as not free of pathogens, except for persons who were unable to expectorate sputum despite sputum induction.

Abbreviations: ALIS: liposomal amikacin for inhalation; ANCOVA: analysis of covariance; ITT: Intention-To-Treat; LSM: Least Square Means; LOCF: last observation carried forward; MMRM: Mixed-model repeated measure; CI: Confidence interval; m: Meters, MDR: Multi-drug regimens (antibiotic combination therapy); SD: Standard deviation; SE: Standard error.

Endpoint	ALIS + MDR N = 224		MDR N = 112		ALIS + MDR vs MDR
	N (%)	Mean value or LSM	N (%)	Mean value or LSM	LSM Difference [95% CI] p value
6-minute walk					
Baseline, mean (SD)	220 (98.2)	425.7 (127.6)	111 (99.1)	420.4 (126.7)	-
Month 6, change from baseline LSM (SE) [a)]	167 (74.6)	-1.8 (12.6)	103 (92.0)	0.9 (13.7)	-2.7 [-21.8; 16.4] 0.78

(a) Missing values were multiply imputed under the assumption of missing-not-at-random using a pattern mixture model. It was assumed that missing values in the ALIS+MDR group followed the target size distribution in the MDR group. Values were not imputed for one subject randomised to the ALIS+MDR group because, as determined by investigators, the subject did not receive study medication and did not complete a baseline visit. The number of imputations performed was not reported.
Effect estimates and p-value are based on an ANCOVA model with treatment arm and stratum of randomisation as fixed effects and baseline values of 6-minute walk distance as covariates.

Endpoint	ALIS + MDR N = 224		MDR N = 112		ALIS + MDR vs MDR
	N (%)	Mean value or LSM	N (%)	Mean value or LSM	LSM Difference [95% CI] p value
Abbreviations: ALIS: liposomal amikacin for inhalation; ANCOVA: analysis of covariance; LSM: Least Square Means; CI: Confidence interval; m: Meters, MDR: Multi-drug regimens (antibiotic combination therapy); SD: Standard deviation; SE: Standard error.					

Quality of life

There are no evaluable data.

Side effects

Endpoint	ALIS + MDR		MDR		ALIS + MDR vs MDR
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95%- CI] p value
AE up to month 8					
EU	223	216 (96.9)	112	98 (87.5)	-
SAE	223	42 (18.8)	112	16 (14.3)	1.48 [0.83; 2.64] 0.18
Severe AE (CTCAE ≥ 3)	223	43 (19.3)	112	12 (10.7)	2.09 [1.10; 3.96] 0.02
EU, which led to the discontinuation of the study medication	223	42 (18.8)	112	1 (0.9)	23.21 [3.19; 168.70]; 0.002
AE with incidence ≥ 10% in at least one treatment arm SOC PT					
Respiratory, thoracic and mediastinal disorders	223	195 (87.4)	112	56 (50.0)	n. d.
- Dysphonia	223	103 (46.2)	112	2 (1.8)	n. d.
- Cough	223	84 (37.7)	112	17 (15.2)	n. d.
- Dyspnoea	223	47 (21.1)	112	9 (8.0)	n. d.
- Haemoptysis	223	39 (17.5)	112	15 (13.4)	n. d.
- Pain in the oropharynx	223	24 (10.8)	112	2 (1.8)	n. d.
Infections and infestations	223	93 (41.7)	112	48 (42.9)	n. d.
Gastrointestinal disorders	223	84 (37.7)	112	24 (21.4)	n. d.
Diarrhoea	223	27 (12.1)	112	5 (4.5)	n. d.

Endpoint	ALIS + MDR		MDR		ALIS + MDR vs MDR
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95%- CI] p value
- Nausea	223	25 (11.2)	112	4 (3.6)	n. d.
General disorders and administration site conditions	223	73 (32.7)	112	16 (14.3)	n. d.
- Fatigue	223	35 (15.7)	112	7 (6.3)	n. d.
Musculoskeletal, connective tissue and bone diseases	223	50 (22.4)	112	17 (15.2)	n. d.
Nervous system disorders	223	51 (22.9)	112	12 (10.7)	n. d.
Skin and subcutaneous tissue disorders	223	40 (17.9)	112	12 (10.7)	n. d.
Investigations, examinations	223	32 (14.4)	112	13 (11.6)	n. d.
Ear and labyrinth disorders	223	33 (14.8)	112	10 (8.9)	n. d.
Eye diseases	223	26 (11.7)	112	7 (6.3)	n. d.
Metabolism and nutrition disorders	223	23 (10.3)	112	11 (9.8)	n. d.
SAE with incidence ≥ 5% in at least one treatment arm SOC					
Respiratory, thoracic and mediastinal disorders	223	25 (11.2)	112	10 (8.9)	n. d.
Infections and infestations	223	19 (8.5)	112	6 (5.4)	n. d.
AE of special interest [a] with incidence ≥ 10% in at least one treatment arm					
Other respiratory events [b]	223	168 (75.3)	112	42 (37.5)	n. d.
Bronchospasm [c]	223	64 (28.7)	112	11 (9.8)	n. d.
Ototoxicity [d]	223	39 (17.5)	112	10 (8.9)	n. d.
Infectious exacerbation of the underlying disease [e]	223	32 (14.3)	112	11 (9.8)	n. d.

a) AEs of special interest were defined a-priori in the statistical analysis plan and are composed of PTs from different SOCs. Haemoptysis, which is also an AE of special interest, is not listed again.
b) PTs from SOC "Respiratory, thoracic, and mediastinal disorders" were included.
c) PTs from SOC "Respiratory, thoracic, and mediastinal disorders" and SOC "Investigations" were included.
d) PTs from SOC Ear and labyrinth disorders and SOC Nervous system disorders were included.
e) PTs from SOC "Respiratory, thoracic, and mediastinal disorders" and SOC "Infections and parasitic diseases" were included.

Abbreviations: ALIS: liposomal amikacin for inhalation; n.d.: no data; CI: Confidence interval; MDR: Multi-drug regimens (antibiotic combination therapy); CTCAE: National Cancer Institute - Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred term according to MedDRA; SOC: System organ class according to MedDRA; (S)AE: (serious) adverse event(s).

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

Treatment of non-tuberculous mycobacterial (NTM) pulmonary infections caused by *Mycobacterium avium* Complex (MAC) in adults with limited treatment options, who do not have cystic fibrosis

approx. 350 to 760 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 Arikayce (active ingredient: amikacin) at the following publicly accessible link (last access: 21 January 2021):

https://www.ema.europa.eu/en/documents/product-information/arikayce-liposomal-product-information_de.pdf

Initiation and monitoring of treatment with liposomal amikacin for inhalation should only be performed by physicians experienced in the treatment of patients with non-tuberculous pulmonary diseases caused by pathogens belonging to the *Mycobacterium avium Complex*.

The patient passport enclosed with the medicinal product in the outer carton informs patients that the use of Arikayce liposomal may be associated with the occurrence of allergic alveolitis.

If sputum culture conversion has not been achieved after a maximum of 6 months of treatment, treatment with liposomal amikacin for inhalation should be discontinued.

4. Treatment costs

Annual treatment costs:

The annual treatment costs shown refer to the first year of treatment.

Treatment of non-tuberculous mycobacterial (NTM) pulmonary infections caused by *Mycobacterium avium* Complex (MAC) in adults with limited treatment options, who do not have cystic fibrosis

Name of therapy	Annual treatment costs/patient
Amikacin	€ 159,350.79
additionally required SHI services	non-quantifiable

costs after deduction of statutory rebates (LAUER-TAXE®, as last revised: 1 May 2021).

II. The resolution will enter into force on the day of its publication on the internet on the G-BA website on 20 May 2021.

The justification for this resolution will be published on the GB-A website at www.g-ba.de.

Berlin, 20 May 2021

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

Prof. Hecken