Justification

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

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of a rare disease (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a paragraph 1, sentence 11, first 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 Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, second half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, first half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an evaluation of the orphan drug in accordance with the principles laid down in Section 35a paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds €50 million in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a paragraph 1 sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the authorisation studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the legal limit of €50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a paragraph 1, sentence 12 SGB V). According to Section 35a paragraph 2 SGB V, the assessment by the G-BA must be

completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The medicinal product Arikayce liposomal containing the active substance amikacin (in liposomal formulation for inhalation) was placed on the market for the first time on 1 December 2020. Relevant date according to Chapter 5, Section 8, paragraph 1, number 7 of the Rules of Procedure of the G-BA (VerfO) for the start of the evaluation procedure for the active substance Amikacin is within three months of the request by the G-BA. If the medicinal product has not yet been placed on the market at that time, the procedure shall start on the date on which it is first placed on the market.

The Subcommittee on Medicinal Products of the Federal Joint Committee (G-BA) decided on 20 March 2018 to initiate a benefit assessment for amikacin in the indication *Mycobacterium avium complex* (MAC) pulmonary infections in accordance with Section 35a (6) SGB V in conjunction with Chapter 5, Section 16 (1) VerfO.

The final dossier was submitted to the G-BA in due time on 27 November 2020. On 1 December 2020, the evaluation process started.

Amikacin for the treatment of Mycobacterium avium complex (MAC) lung infections is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with section 35a, paragraph 1, sentence 11, 1st half of the sentence of the sentence German Social Code, Book Five (SGB V), the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the authorisation studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 1 March 2021 together with the IQWiG assessment on the the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA made its decision on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G20-29) and the statements made in the written statements and oral hearing process, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of amikacin

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

1 General Methods, version 6.0 of 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of amikacin (Arikayce liposomal) in accordance with the product information

Arikayce liposomal is indicated t 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 approved therapeutic indication

2.1.2 Extent of the additional benefit and the significance of the evidence

In summary, the additional benefit of amikacin is assessed as follows:

Adult patients with pulmonary infections caused by non-tuberculous mycobacteria (NTM) belonging to the Mycobacterium avium complex (MAC), with limited treatment options, who do not have cystic fibrosis.

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

Purpose:

The pharmaceutical company presents results of the CONVERT study on which the approval of liposomal amikacin for inhalation is based.

CONVERT is a multicenter, open-label, randomised study to evaluate the efficacy and safety of liposomal amikacin for inhalation as an adjunct to a multi-medicinal product regimen (MDR)(N = 224) compared to MDR alone (N = 112) in adult patients with pulmonary *Mycobacterium avium complex*(MAC) pulmonary infection and without cystic fibrosis. Patients had to have been positive for MAC culture after treatment with MDR from at least 2 different antibiotics for a minimum of 6 consecutive months. For baseline characteristics, imbalances were particularly evident in gender distribution (73.7% female patients in the intervention arm vs 60.7% in the control arm), in the proportion of patients with a three-agent MDR (65% in the intervention arm vs 75% in the control arm), in the average duration of disease, and in the proportion of patients with chronic obstructive pulmonary disease (22% in the intervention arm vs 33% in the control arm). The use of beta-2-adrenoceptor agonists as part of concomitant medication differed between study arms (51.3% in the intervention arm vs 39.3% in the control arm) during the study.

A minimum 10-week screening phase was followed by the treatment phase, during which sputum samples were collected monthly up to month 6. Based on sputum culture results at month 6, study participants were divided into converters (at least 3 consecutive negative sputum cultures) or non-converters at the study visit at month 8. Converters continued treatment for 12 months (calculated from the date of the first of three consecutive negative sputum cultures) according to their assigned study arm. This was followed by a one-year follow-up period.

Non-converters and converters with renewed positive pathogen detection at month 6 abandoned the CONVERT study at month 8. This was the case for 71% of the intervention group and 91% of the control group. These patients were allowed to cross over into an open single-arm extension study. Over the entire study period, 27% of the intervention group and 13% of the control group terminated the study prematurely.

For the benefit assessment, only the comparative data collected up to month 8 can be used, as the data were no longer collected after month 8 for a large proportion of the randomised

patients, which means that the ITT principle is no longer guaranteed and the data can only be assessed to a very limited extent.

Mortality

The mortality data presented at month 8 show only small numbers of deaths (3 each per study arm: Amikacin+MDR: 1.3%; MDR: 2.7%), but no effect estimates were provided. Due to the study design, the results collected after month 8 are considered to be potentially highly biased and are not suitable for the assessment of additional benefit.

Morbidity

Freedom from pathogens:

Evidence of pathogen clearance is based on patient sputum samples.

Therefore, the endpoint is to be considered a laboratory parameter and represents a surrogate parameter that is not per se relevant to the patient. Surrogate validation data were not provided. In the present indication, freedom from pathogens is a necessary prerequisite for improvement of pulmonary MAC infection, which is why the endpoint can be considered in addition for the benefit assessment. For a viable assessment in the context of the benefit assessment, additional comparative data would be required that at least show an improvement in symptoms or quality of life associated with freedom from the pathogen. However, no such data were provided.

The primary study endpoint in the statistical analysis plan valid for the European approval procedure was defined as the proportion of individuals achieving sustained freedom from pathogens three months after discontinuation of all treatment. In addition, achievement of sputum conversion, defined as at least 3 consecutive negative sputum cultures, by month 6, pathogen freedom 12 months on treatment after sputum conversion, and pathogen freedom 12 months after discontinuation of all treatment will be considered.

From the limitations of the study it follows that the course of pathogen freedom can only be considered in the converters. The various analyses carried out come to similar conclusions overall. There are statistically significant effects in favour of amikacin. The proportion of patients who were pathogen positive at baseline and pathogen-free after 12 months of treatment was 18.3%. At 3 months after the end of treatment, 16.1% of patients were still pathogen-free, and at the end of the 12-month follow-up period, only 13.4% of patients were still pathogen-free.

The endpoints relapses and new infections were only evaluated descriptively in the study and are not used for the benefit assessment.

6-minute walk

Walking distance walked within 6 minutes, collected according to the American Thoracic Society guideline, is considered patient-relevant. The potential for bias for the analysis of the 6-minute walk distance is rated as high because it is unclear whether blinding of study personnel to the 6-minute walk test could be maintained in the otherwise unblinded study, and because of the significantly increased proportion of missing values in the intervention arm. Analyses are available at month 6 and month 8, although the analysis at month 8 was defined only as an exploratory endpoint in the study protocol. Missing values (approximately 25% at month 6) were accounted for in the statistical models using multiple imputation. Overall, the analyses performed showed no statistically significant difference between the study arms.

EQ-5D VAS

The patient's assessment of their health status is a patient-relevant endpoint, and the survey using the visual analogue scale (VAS) of the EQ-5D questionnaire is considered adequate. In the study, the endpoint was collected at baseline and at multiple time points during and after

treatment. However, due to the difference of more than 15% in the proportion of missing values (proportion of missing values at month 6 in the intervention arm 24% and in the control arm 6%), the results are considered highly biased. An imputation of missing values was not performed by the pharmaceutical company. Therefore, the endpoint cannot be conclusively assessed and cannot be used for the benefit assessment.

Quality of life

Health-related quality of life was assessed in the study using St. George's Respiratory Questionnaire (SGRQ). The study collected the endpoint at baseline and at multiple time points during and after treatment; statistical analyses were presented at month 6 and at month 8 using the mean differences.

However, due to the difference of more than 15% in the proportion of missing values (proportion of missing values at month 6 in the intervention arm 25% and in the control arm 7%), the results are considered highly biased. An imputation of missing values was not performed by the pharmaceutical company. Therefore, the endpoint cannot be conclusively assessed and cannot be used for the benefit assessment.

Side effects

Up to the time of evaluation at month 8, there were statistically significant differences in the study to the disadvantage of amikacin therapy with regard to serious adverse events (AEs, CTCAE grade ≥ 3) and AEs that led to therapy discontinuation.

No data are available on the severe AEs that occurred at month 8, so it remains unclear which severe AEs (at SOC or PT level) account for the difference between study arms. There were no statistically significant differences in serious AE (SAE).

Among AEs with incidence ≥ 10% in at least one treatment arm, there are numerical disadvantages for amikacin (differences of at least 10% between treatment arms) in SOC "Respiratory, thoracic and mediastinal disorders" (here for PT Dysphonia, cough and dyspnoea), "Gastrointestinal disorders", "General disorders and complaints at the site of administration" and "Nervous system disorders". No statistical analysis was provided.

In addition, for AEs of special interest with incidence ≥ 10% in at least one treatment arm, numerical disadvantages were seen for bronchospasm, haemoptysis, ototoxicity, infectious exacerbation of underlying disease, and other respiratory events. No statistical analysis was provided.

Overall view:

For the benefit assessment of liposomal amikacin for inhalation for the treatment of MAC pulmonary infections in adult patients with limited treatment options who do not have cystic fibrosis, the results of the CONVERT study will be used. Comparative data of a therapy with amikacin as an add-on to an antibiotic combination treatment versus such a combination treatment alone are only available up to month 8 due to the study design. After month 8, only those patients who were classified as converters continued to receive the study medication, resulting in a large proportion of patients exiting the study. The data collected after month 8 can therefore only be interpreted to a very limited extent.

Results on mortality, morbidity, and side effects are available. In the Mortality category, there are only small numbers of cases and no evidence of advantages or disadvantages in the amikacin study arm. In the Morbidity category, data are available in particular on the absence of pathogens. The endpoint is to be considered a surrogate laboratory parameter, but no surrogate validation was provided for this. A large proportion of pathogen-free patients suffer a relapse or reinfection. The data from the intervention group show that a proportion of patients of about 13.4% remain free of pathogens even one year after the end of therapy. However, the study did not show an effect of freedom from pathogens on other patient-relevant endpoints of morbidity or quality of life. Data on symptom improvement and/or improvement in quality of life

would be required to assess pathogen clearance as a prerequisite for improvement in MAC pulmonary infection. Evaluations of the 6-minute walk distance showed no statistically significant differences between treatment arms.

For adverse events, results are available to the disadvantage of amikacin for AEs leading to treatment discontinuation and for severe AEs up to month 8.

In summary, although there is a small proportion of patients who remain pathogen-free for prolonged periods under inhaled amikacin therapy. However, due to the study design, no assessable comparative data on symptom improvement, quality of life and safety are available beyond month 8, which means that the above-mentioned proportion cannot be used to quantify the additional benefit. The available comparative data (up to month 8 of treatment) also show no symptomatic improvement and also an increased incidence of side effects. Therefore, overall, there is no evidence base to quantify the additional benefit of liposomal amikacin for inhalation in pulmonary MAC infections.

Significance of the evidence

The significance is limited in particular due to the study design, which does not allow any comparative statements to be made with respect to standard antibiotic therapy after the 8th day of treatment. Month of treatment allowed, as at this time the patients with positive sputum control (non-converters) left the study.

The severity of the underlying pulmonary disease makes it difficult to assess the evidence on morbidity, especially in light of the unblinded study design. In addition, there are imbalances in the gender distribution and in the proportion of patients with obstructive diseases between the study arms.

Overall, the significance of the evidence can only be taken as a hint

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the active ingredient amikacin in liposomal formulation. Amikacin was approved in this formulation as an orphan drug for the treatment of pulmonary infections caused by non-tuberculous *mycobacteria* (NTM) belonging to the *Mycobacterium avium Complex* (MAC) in adults with limited treatment options who do not have cystic fibrosis.

For this patient group, the pharmaceutical entrepreneur presents the multicenter, open, randomised study CONVERT. This is a study to investigate the efficacy and safety of liposomal amikacin for inhalation as an adjunct to multi-drug regimen (MDR) antibiotic therapy compared to MDR alone.

For the benefit assessment, only the comparative data collected up to month 8 can be used, as the survey was no longer conducted after month 8 for a large proportion of the randomised patients, which means that the data can only be assessed to a very limited extent.

In the Mortality category, there is no evidence of advantages or disadvantages in amikacin.

Freedom from pathogens data were collected in the study. However, for an assessment of freedom from the pathogen as improvement in MAC pulmonary infection would require additional data on improvement in symptomatology and/or quality of life. Evaluations of the 6-minute walk distance showed no statistically significant differences between treatment arms.

By month 8, an increased incidence of side effects is observed with Amikacin.

The significance is limited in particular due to the study design, which does not allow comparative statements to be made with MDR after the 8th month of treatment.

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

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients approx. 350 – 760 is based on the target population in statutory health insurance (SHI). The information follows the representations of the pharmaceutical company. Uncertainties exist in the correct identification of patient cases in the routine data analyses and due to the expert estimate used with large variation in prevalence figures for pulmonary infections with non-tuberculous mycobacteria (NTM) in different regions of Germany. In addition, the proportion of 74% treatment-naive individuals applied by the pharmaceutical company is uncertain, as the proportion of treated patients with a MAC pulmonary infection cannot be reliably derived from the routine data used.

Finally, there is uncertainty in the proportion of patients with limited treatment options (the pharmaceutical company assumes a proportion of 39%), as the transferability of the results of the studies used in the data analysis, most of which originated in Japan, to the German health care context is questionable due to the different distribution of MAC isolates worldwide.

2.3 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.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 May 2021).

The use of Arikayce liposomal is limited to 18 months.

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

Treatment duration:

Name of therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Amikacin	1 x daily	365	1	365

Consumption:

Name of therapy	Dosage/ application	Dosage/patient/days of treatment	Usage by strength/ day of treatment	Treatment days patient/ year	Average annual consumption by strength
Medicinal product to be assessed					
Amikacin	590 mg	590 mg	1 x 590 mg	365	365 x 590 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular strength was first determined on the basis of consumption. To calculate the annual treatment costs, the required number of packs of a particular strength was first determined on the basis of consumption. Having determined the number of packs of a particular strength, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

Name of therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Amikacin	28 LOV	€ 12,965.84	€ 1.77	€ 739.90	€ 12,224.17
Abbreviations: LOV = solution for a nebuliser					

LAUER-TAXE® last revised: 1 May 2021

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information or patient information leaflet, the differences incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Arikayce liposomal may only be used with the Lamira inhalation system (nebuliser, aerosol generator and control unit (base controller)) according to the product information. Nebuliser and aerosol generator are included in the package. The Base Controller control unit required in addition is reimbursed on the basis of cash register-specific contract prices. Since the product is not listed in the Lauer-Taxe, no exemplary price is listed here.

3. Bureaucratic costs

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

On 27 November 2020, the pharmaceutical company submitted a dossier for the benefit assessment of amikacin to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 7 VerfO.

The benefit assessment of the G-BA was published on 1 March 2021 together with the IQWiG assessment of treatment costs and patient numbers on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting the written statements was 22 March 2021.

The oral hearing was held on 06 April 2021.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the comments procedure was submitted on 28 April 2021.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the meetings.

The evaluation of the written statements received and the oral hearing were discussed at the meeting of the subcommittee on 11 May 2021, and the draft resolution was approved.

At its meeting on 20 May 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	10 March 2021	Information of the benefit assessment of the G-BA
Working group Section 35a	31 March 2021	Information on written statement procedures received; preparation of the oral hearing
Subcommittee Medicinal products	06 April 2021	Conduct of the oral hearing
Working group Section 35a	14 April 2021 5 May 2021	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	11 May 2021	Concluding consultation of the draft resolution
Plenum	20 May 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 20 May 2021

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

Prof. Hecken