Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Ceftolozane/ tazobactam (new therapeutic indication: bacterial infections, multiple therapeutic indications, < 18 years)

of 15 August 2022

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.

Pursuant to Section 35a, paragraph 1c, sentence 1 SGB V, the Federal Joint Committee shall exempt the pharmaceutical company from the obligation to submit the evidence pursuant to Section 35a, paragraph 1, sentence 3, numbers 2 and 3 SGB V (medical benefit and additional medical benefit in relation to the appropriate comparator therapy) upon request, if it is an antibiotic that is effective against infections caused by multi-resistant bacterial pathogens with limited treatment options and the use of this antibiotic is subject to a strict indication (reserve antibiotic).

The additional benefit is deemed to be proven if the Federal Joint Committee has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the Federal Joint Committee.

By resolution pursuant to Section 35a, paragraph 3, sentence 1 SGB V, the Federal Joint Committee shall specify the requirements for a quality-assured application of the reserve antibiotic pursuant to Section 35a, paragraph 1c, sentence 8 SGB V, taking into account the effects on the resistance situation. Pursuant to Chapter 5, Section 20, paragraph 6, sentence 3 of the Rules of Procedure (VerfO), the Federal Joint Committee may lay down restrictive requirements for the use of the antibiotic in order to ensure a strict indication, if this is necessary to maintain the reserve status of the medicinal product. With regard to these requirements for a quality-assured application of the reserve antibiotic, it shall obtain a statement from the Robert Koch Institute, which shall be prepared in agreement with the Federal Institute for Drugs and Medical Devices.

Pursuant to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment, taking into account the requirements for a quality-assured application according to Section 35a, paragraph 1c, sentence 8 SGB V, within three months of its publication. The resolution is to be published online and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

By resolution of 20 January 2022, the Federal Joint Committee decided that the pharmaceutical company is exempted from the obligation to submit evidence in the benefit assessment procedure for the medicinal product Zerbaxa with the combination of active ingredients ceftolozane/ tazobactam according to Section 35a, paragraph 1, sentence 3, numbers 2 and 3 SGB V, since the medicinal product Zerbaxa with the combination of active ingredients ceftolozane/ tazobactam for the treatment of bacterial infections is a reserve antibiotic within the meaning of Section 35a, paragraph 1c, sentence 1 SGB V.

The combination of active ingredients ceftolozane/ tazobactam (Zerbaxa) was listed for the first time on 1 December 2015 in the "LAUER-TAXE®", the extensive German registry of available medicinal products and their prices.

On 25 July 2022, Zerbaxa received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 12 August 2022, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, No.2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the combination of active ingredients ceftolozane/ tazobactam with the new therapeutic indication (bacterial infections in paediatric patients) in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication). In this, the pharmaceutical company submitted evidence pursuant to Section 35a, paragraph 1, sentence 3, numbers 1, 4 and 5 SGB V and evidence on the requirements for a quality-assured application of the reserve antibiotic, taking into account the effects on the resistance situation (Chapter 5 VerfO Annex II. 1 Section 1.4). The assessment procedure started on 15 August 2022.

The additional benefit is deemed to be proven if the Federal Joint Committee has decided on an exemption for a reserve antibiotic in accordance with Section 35a paragraph 1c sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the Federal Joint Committee. The exemption from the obligation to submit the evidence according to Section 35a, paragraph 1, sentence 3, numbers 2 and 3 SGB V applies to the medicinal product with the therapeutic indication authorised at the time of application and subsequently granted new therapeutic indications within the meaning of Section 2, paragraph 2, Chap. 5, Section 15a, paragraph 5 sentence 1 VerfO. By resolution pursuant to Section 35a, paragraph 3, sentence 1 SGB V, the Federal Joint Committee shall specify requirements for a quality-assured application of the reserve antibiotic, taking into account the effects on the resistance situation.

A draft of the requirements for a quality-assured application of the reserve antibiotic was made available to the Robert Koch Institute for drafting a statement in agreement with the BfArM in accordance with Section 35a, paragraph 1c SGB V.

The G-BA commissioned the IQWiG to assess the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers.

The draft of the requirements for a quality-assured application as well as the RKI statement drafted in agreement with the BfArM were published on the G-BA's website (www.g-ba.de) together with IQWiG's assessment of treatment costs and patient numbers, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the draft of the requirements for a quality-assured application prepared by the G-BA taking into account the joint statement of RKI/BfArM, the IQWiG's assessment of treatment costs and patient numbers (IQWiG G22-27) and the statements submitted in the written statement and oral hearing procedure.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of ceftolozane/ tazobactam (Zerbaxa) according to the product information

Zerbaxa is indicated for the treatment of the following infections in adult and paediatric patients:

- Complicated intra-abdominal infections;
- Acute pyelonephritis;
- Complicated urinary tract infections.

Zerbaxa is also indicated for the treatment of the following infection in adult patients (18 years or older):

- Hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP).

Consideration should be given to official guidelines on the appropriate use of antibacterial agents.

Therapeutic indication of the resolution (resolution of 2 February 2023):

Zerbaxa is indicated for the treatment of the following infections in paediatric patients:

- Complicated intra-abdominal infections;
- Acute pyelonephritis;
- Complicated urinary tract infections.

2.1.2 Extent of the additional benefit and significance of the evidence

In summary, the additional benefit of ceftolozane/ tazobactam is assessed as follows:

a) Paediatric patients with complicated intra-abdominal infections

The additional benefit is considered proven.

b) Paediatric patients with acute pyelonephritis

The additional benefit is considered proven.

c) Paediatric patients with complicated urinary tract infection

The additional benefit is considered proven.

Justification:

For the medicinal product Zerbaxa with the combination of active ingredients ceftolozane/ tazobactam, an exemption from the obligation to submit the evidence according to Section 35a paragraph 1 sentence 3 number 2 and 3 SGB V was granted by resolution of 20 January 2022, as it is a reserve antibiotic within the meaning of Section 35a paragraph 1c sentence 1 SGB V.

The additional benefit is deemed to be proven if the Federal Joint Committee has decided on an exemption for a reserve antibiotic in accordance with Section 35a paragraph 1c sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the Federal Joint Committee.

2.1.3 Summary of the assessment

Ceftolozane/ tazobactam is approved for the treatment of the following infections in paediatric patients:

- Complicated intra-abdominal infections;
- Acute pyelonephritis;
- Complicated urinary tract infections;

3 patient groups were formed according to the individual therapeutic indications.

The additional benefit of ceftolozane/ tazobactam is assessed for each of the patient groups as follows:

For the medicinal product Zerbaxa with the combination of active ingredients ceftolozane/ tazobactam, an exemption from the obligation to submit the evidence according to Section 35a paragraph 1 sentence 3 number 2 and 3 SGB V was granted by resolution of 20 January 2022, as it is a reserve antibiotic within the meaning of Section 35a, paragraph 1c, sentence 1 SGB V.

The additional benefit is deemed to be proven if the Federal Joint Committee has decided on an exemption for a reserve antibiotic in accordance with Section 35a paragraph 1c sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the Federal Joint Committee.

By resolution pursuant to Section 35a, paragraph 3, sentence 1 SGB V, the Federal Joint Committee specified the requirements for a quality-assured application of the reserve antibiotic pursuant to Section 35a, paragraph 1c, sentence 8 SGB V, taking into account the effects on the resistance situation.

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

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The resolution is based on the information from the dossier assessment of the IQWiG (mandate G22-27). The calculation of patient numbers was based on the assumption that the target population mainly comprises pathogens with limited treatment options - operationalised via the presence of carbapenem-resistant *Pseudomonas aeruginosa*. The patient numbers given tend to be underestimated, primarily due to the restriction to this pathogen in the derivation of the figures. Further uncertainties arise from the procedure for identifying paediatric cases using the selected ICD codes.

However, a lower number of patients in the SHI target population may result particularly against the background of the restrictive use of ceftolozane/ tazobactam within the framework of a quality-assured application as a reserve antibiotic.

2.3 Requirements for a quality-assured application

By resolution pursuant to Section 35a, paragraph 3, sentence 1 SGB V, the Federal Joint Committee shall specify requirements for a quality-assured application of the reserve antibiotic, taking into account the effects on the resistance situation. The requirements for a quality-assured application are based on the draft prepared by the Federal Joint Committee and the statement of the Robert Koch Institute, which was prepared in agreement with the BfArM. The statements made in the written statement and oral hearing procedure were taken into account.

About the notes on application

Reference is made to the specifications of the marketing authorisation. The requirement that ceftolozane/ tazobactam may only be used for the treatment of infections mentioned in the therapeutic indication if only limited treatment options are available is specified in the present resolution within the framework of the requirements for a quality-assured application in order to ensure the strict indication pursuant to Section 35a, paragraph 1c SGB V.

According to the field of expertise, qualified consultation takes place with a specialist in the field of infectiology (internal medicine and infectiology[1], microbiology, virology and epidemiology of infectious diseases or additional qualification in infectiology) or, if not available, with a specialist from other disciplines who must have appropriate experience in the treatment of infectious diseases with multi-drug resistant pathogens. In this context, the wording "in case of unavailability" illustrates the special importance of the field of infectiology.

About the notes on pathogen detection

In principle, ceftolozane/ tazobactam should not be used as part of a calculated (empirical) therapy. The strict indication as a reserve antibiotic requires knowledge of the pathogen. Even in the exceptional cases mentioned, infection with a multi-drug resistant aerobic Gram-negative pathogen is at least probable. As a rule, pathogen detection can be expected after 72 hours at the latest. If the pathogen detection reveals that the pathogen is sensitive to other antibiotics (without reserve status), the therapy must be de-escalated accordingly to avoid unnecessary use of the reserve antibiotic. An empirical therapy with ceftolozane/ tazobactam should be as short as possible.

[1] Further training to become a specialist in internal medicine and infectiology was included in the sample further training regulations of the German Medical Association in 2021.

About the instructions for implementation

In order to implement the requirements for a quality-assured application, it is necessary that they are taken into account in the hospital's internal regulations/ processes.

The respective Drug Commission is responsible for integration into the processes. Evidence-based antibiotic stewardship teams (see S3 guideline: strategies to ensure rational antibiotic use in hospitals, update 2018) are particularly suitable for implementation.

Pursuant to Section 23 paragraph 4 Infection Protection Act, the treatment facility is obliged to carry out consumption and resistance surveillance, whereby there is no specification of the systems to be used. The use of a uniform system is necessary for the future assessment of the resistance and consumption situation. The RKI's ARS, AVS and ARVIA systems aggregate Germany-wide data on antibiotic resistance and consumption. ARS also forms the basis for Germany's participation in international surveillance systems.[2] For this reason, the participation of clinics using ceftolozane/ tazobactam in these systems should be sought.

If there has been no participation to date, the data must be reported to the above-mentioned systems at least for the reserve antibiotic ceftolozane/ tazobactam.

A transitional period until 1 January 2024 is considered appropriate for this.

Until participation in the mentioned systems, consumption and resistance situation must be ensured via the existing systems.

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: 15 January 2023).

Ceftolozane/ tazobactam (Zerbaxa) is listed in the LAUER-TAXE®, but is only dispensed as a clinic pack. Accordingly, the active ingredient is not subject to the Pharmaceutical Price Ordinance (Arzneimittelpreisverordnung) and no rebates according to Section 130 or Section 130a SGB V apply. The calculation is based on the purchase price of the clinic pack plus 19% value added tax, in deviation from the LAUER-TAXE® data usually taken into account.

To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack plus value added tax.

Treatment period:

The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

According to the product information, treatment with ceftolozane/ tazobactam may be required for 5 to 14 days, depending on the therapeutic indication.

[2] Information at https://ars.rki.de/

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Ceftolozane/ tazobactam				
Therapeutic indication a) cIAI	3 x daily	5 – 14	1	5 – 14
Therapeutic indication b) cUTI	3 x daily	7 – 14	1	7 – 14
Therapeutic indication c) pyelonephritis	3 x daily	7 – 14	1	7 – 14

Consumption:

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments, e.g. because of side effects or comorbidities, are not taken into account when calculating the annual treatment costs.

For the calculation of dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied to children aged one and older (average body weight of 17-year-olds: 67.0 kg).[3] For children under one year of age, the reference percentiles of the Robert Koch Institute were used. Based on the average body weights of boys and girls, the average body weight for children aged 0 months is 3.46 kg.[4]

The (daily) doses recommended in the product information were used as the calculation basis.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Ceftolozane/ tazobactam					
Therapeutic indication a) cIAI Therapeutic indication b) cUTI	20 mg/kg /10 mg/kg - 1 g/ 0.5 g	3 x 69.2 mg/ 34.6 mg –	3 x 1 g/ 0.5g[5]	5 – 14 7 – 14	15 x 1 g/ 0.5 g – 42 x 1 g/ 0.5 g 21 x 1 g/ 0.5 g – 42 x 1 g/ 0.5 g

[3] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

[4] Robert Koch Institute. Contributions to Federal Health Reporting: Reference percentiles for anthropometric measures and blood pressure from the Study on the Health of Children and Adolescents in Germany (KiGGS) [online]. [Accessed: 19.12.2022]. URL: https://www.rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GBEDownloadsB/KiGGS_Referenzperzentile.pdf?__blob=publicationFile

[5] Based on the following information in the Zerbaxa product information (as of July 2022), the remainder of each vial is discarded after drawing the volume for infusion:
- Each vial is for single use only.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Therapeutic indication c) pyelonephritis		3 x 1 g/ 0.5 g		7 – 14	21 x 1 g/ 0.5 g – 42 x 1 g/ 0.5 g

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (clinic purchase registry)	Value added tax (19%)	Costs of the medicinal product
Medicinal product to be assessed				
Ceftolozane/ tazobactam 1 g/ 0.5 g	10 PIC	€ 915.00	€ 173.85	€ 1,088.85
Abbreviations: PIC = powder for the preparation of an infusion solution concentrate				

LAUER-TAXE® last revised: 15 January 2023

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, the costs 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.

2.5 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 Ceftolozane/ tazobactam

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

3. Bureaucratic costs calculation

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 12 August 2022, the pharmaceutical company submitted a dossier for the benefit assessment of ceftolozane/ tazobactam to the G-BA in due time.

The draft of the G-BA's requirements for a quality-assured application was published on the G-BA's website (www.g-ba.de) on 15 November 2022 together with the Robert Koch Institute's statement and IQWiG's assessment of treatment costs and patient numbers, thus initiating the written statement procedure. The deadline for submitting written statements was 6 December 2022.

The oral hearing was held on 19 December 2022.

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 sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 24 January 2023, and the proposed resolution was approved.

At its session on 2 February 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Working group Section 35a	31 August 2022	Consultation on the draft requirements for a quality-assured application
Subcommittee Medicinal products	6 September 2022	Draft requirements for a quality-assured application; notification of the RKI and the BfArM
Subcommittee Medicinal products	25 October 2022	Draft requirements for a quality-assured application under consideration of the statement of the Robert Koch Institute
Working group Section 35a	14 December 2022	Information on written statements received; preparation of the oral hearing

Subcommittee Medicinal products	19 December 2022	Conduct of the oral hearing
Working group Section 35a	4 January 2023 18 January 2023	Consultation on the draft requirements for a quality-assured application of 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	24 January 2023	Concluding discussion of the draft resolution
Plenum	2 February 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 August 2022

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

Prof. Hecken