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 Cefiderocol (infections due to aerobic Gram-negative organisms)

of 5 May 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 on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

By resolution of 21 October 2021, 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 Fetcroja with the active ingredient cefiderocol according to Section 35a, paragraph 1, sentence 3, numbers 2 and 3 SGB V, since the medicinal product Fetcroja with the active ingredient cefiderocol for the treatment of infections due to aerobic Gram-negative pathogens is a reserve antibiotic within the meaning of Section 35a, paragraph 1c, sentence 1 SGB V.

The active ingredient cefiderocol was listed for the first time on 15 January 2021 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices. By resolution of 20 August 2020, the G-BA suspended the application procedure following the receipt of the application on 16 July 2020 for exemption from the obligation to submit evidence according to Section 35a paragraph 1 sentence 3 numbers 2 and 3 SGB V due to reserve antibiotic status pursuant to Section 35a, paragraph 1c SGB V. This resulted in the temporary suspension of the obligation to transmit the dossier according to Chapter 5, Section

11 VerfO. The suspension ended three months after the G-BA's Rules of Procedure (VerfO), adapted on the basis of Section 35a, paragraph 1c, sentence 4 SGB V, took effect, and after publication of the criteria - determined by the Robert Koch Institute (RKI) in agreement with the Federal Institute for Drugs and Medical Devices (BfArM) - for classification as a reserve antibiotic according to Section 35a, paragraph 1c, sentence 5 SGB V. The pharmaceutical company was obliged to submit the grounds for the application in accordance with the adapted regulations in the VerfO on the basis of the criteria of the RKI pursuant to Section 35a, paragraph 1c, sentence 5 SGB V at the latest by the date on which the suspension ends. When the grounds for the application were submitted, restoration to the previous version was granted with effect from the time of the first obligation to submit the evidence in accordance with Section 35a, paragraph 1, sentence 3 SGB V. In a letter dated 6 August 2021, the pharmaceutical company submitted the grounds for its application. By resolution of 21 October 2021 on the exemption pursuant to Section 35a, paragraph 1c, sentence 1 SGB V, the pharmaceutical company was requested to submit a dossier to the G-BA by 1 February 2022 pursuant to Chapter 5, Section 11, paragraph 3 VerfO.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 3 November 2021. 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 November 2021.

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 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 G21-33) 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 Cefiderocol (Fetcroja) in accordance with the product information

Fetcroja is indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.

Therapeutic indication of the resolution (resolution of 5 May 2022):

see the approved therapeutic indication

2.1.2 Additional benefit of the medicinal product

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

Adults with infections due to aerobic Gram-negative organisms with limited treatment options

The additional benefit is considered proven.

Justification:

For the medicinal product Fetcroja with the active ingredient cefiderocol, 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 21 October 2021, 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

Cefiderocol is approved for use in adults for the treatment of infections due to aerobic Gram-negative organisms with limited treatment options.

The additional benefit of cefiderocol is assessed as follows:

Adults with infections due to aerobic Gram-negative organisms with limited treatment options

The additional benefit is considered proven.

For the medicinal product Fetcroja with the active ingredient cefiderocol, 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 21 October 2021, 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 G21-33). The calculation is made using two different approaches based on data from the RKI and the HISS (Hospital Infection Surveillance System) pathogen surveillance, respectively, for 2019.

In the calculation, the limited treatment options were mapped via the presence of carbapenem resistance. The procedure leads to uncertainties as the therapeutic indication does not specify the limited treatment options.

In addition, the derivation is made on the basis of infection cases with various individual pathogens. Since patients can also be infected several times or with more than one pathogen, the number of patients can also be lower than the number of cases.

Further uncertainties result from different operationalisations of carbapenem resistance in the two data bases, from the exclusive consideration of nosocomial infections when considering Pseudomonas aeruginosa infections. The transfer of the percentage of adults in the total population to the number of infections with certain pathogens or to the number of full inpatient cases can lead to an underestimation due to the unequal age distribution of full inpatient cases compared to the total population. In addition, the use of percentage values of the data of the ITS-HISS module leads to uncertainties, since only intensive care cases are taken into account here, but not all inpatients.

The patient numbers are therefore to be assessed as uncertain overall.

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 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 cefiderocol should only be used in adults for the treatment of infections due to aerobic Gram-negative organisms with limited treatment options follows directly from the approved therapeutic indication (section 4.1 of the product information). The recommendation in section 4.2 of the product information refers to medical consultation, which is specified in the following requirements for a quality-assured application.

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, cefiderocol should not be used as part of a calculated (empirical) therapy. The approved therapeutic indication 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. The written and oral statements indicated that, as a rule, a pathogen may be detected 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. Empirical therapy with cefiderocol should be as short as possible.

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 cefiderocol 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 cefiderocol. A transitional period of 6 months is considered appropriate for this.

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

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 April 2022).

Cefiderocol 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:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Cefiderocol	3 x daily	5 - 21	1	5 - 21

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.

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.

Cefiderocol may have to be taken for up to 21 days.

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					
Cefiderocol	2 g	3 x 2 g	6 x 1 g	5 - 21	30 x 1 g - 126 x 1 g

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (Taxe®-clinic- purchase)	Value added tax (19%)	Costs of the medicinal product
Medicinal product to be assessed				
Cefiderocol 1 g	10 PIC	€ 1,500.00	€ 285	€ 1,785.00
Abbreviations: PIC = powder for the preparation of an infusion solution concentrate				

LAUER-TAXE® last revised: 15 April 2022

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.

No additionally required SHI services are taken into account for the cost representation.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the Hilfstaxe in its currently valid version, surcharges for the production of infusion solutions containing antibiotics and virustatics amount to a maximum of € 39 per ready-to-apply unit. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

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 3 November 2021, the pharmaceutical company submitted a dossier for the benefit assessment of cefiderocol to the G-BA in due time in accordance with Chapter 5 Section 8 paragraph 1 number 1 sentence 2 VerfO.

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 February 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 9 March 2022.

The oral hearing was held on 28 March 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 26 April 2022, and the proposed resolution was approved.

At its session on 5 May 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Working group Section 35a	30 November 2021 14 December 2021 1 February 2022	Consultation on the draft requirements for a quality-assured application
Subcommittee Medicinal products	21 December 2021	Draft requirements for a quality-assured application; notification of the RKI and BfArM
Subcommittee Medicinal products	8 February 2022	Draft requirements for a quality-assured application, taking into account the statement of the Robert Koch Institute
Working group Section 35a	15 March 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	28 March 2022	Conduct of the oral hearing

Working group Section 35a	5 April 2022 20 April 2022	Consultation on the requirements for a quality-assured application, the IQWiG's assessment of treatment costs and patient numbers, and the evaluation of the written statement procedure
Subcommittee Medicinal products	26 April 2022	Concluding discussion of the draft resolution
Plenum	5 May 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 5 May 2022

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

Prof. Hecken