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)
Rezafungin (invasive candidiasis)

of 1 August 2024

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 rare diseases (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, 1st half of the sentence German Social Code, Book Five (SGB V). 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, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment 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 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 € 30 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, paragraphs 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 approval 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 turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. 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 relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient rezafungin on 1 February 2024 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. 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 31 January 2024.

Rezafungin for the treatment of invasive candidiasis in adults is approved as a medicinal product for the treatment of rare diseases 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 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 approval 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 2 May 2024 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), 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 dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G24-03) and the statements made in the written statement and oral hearing procedure, 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 approval 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 rezafungin.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Rezafungin (Rezzayo) in accordance with the product information

Rezzayo is indicated for the treatment of invasive candidiasis in adults.

1 General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Therapeutic indication of the resolution (resolution of 1 August 2024):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

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

For adults with invasive candidiasis, there is a hint for a non-quantifiable additional benefit, since the scientific data does not allow quantification.

Justification:

The benefit assessment of rezafungin in this therapeutic indication is based on the pivotal ReSTORE study and the supportive STRIVE study.

ReSTORE (study period 2018-2021) is a multinational, double-blind, randomised, active-controlled phase III study to investigate the efficacy and safety of rezafungin versus caspofungin for the treatment of adults with candidaemia and/or invasive candidiasis. The treatment phase of the ReSTORE study lasted between 14 and 28 days; the last visit took place between day 52 and day 59. 199 patients (N = 100 in the intervention arm and N = 99 in the control arm) were enrolled in the study.

The multinational, exploratory, double-blind, randomised, active-controlled phase II STRIVE study (study period 2016-2019) also compared rezafungin with caspofungin. The study comprised three study phases. For the benefit assessment, the pooled data from the three phases of those patients with dosage compliant with the marketing authorisation were taken into account (N = 57 in the intervention arm and N = 69 in the control arm). The treatment phase of the STRIVE study lasted between ≥14 and ≤21 days for candidaemia and up to 28 days for invasive candidiasis; the last visit took place between days 45 and 52 for candidaemia and between days 52 and 59 for invasive candidiasis.

In both studies, patients aged 18 years and over with a mycologically confirmed diagnosis of candidaemia and/or invasive candidiasis and at least one systemic sign attributable to the disease (e.g. fever, hypothermia, hypotension, tachycardia) were enrolled.

<u>Mortality</u>

Overall survival

Deaths were documented continuously over the entire treatment duration and at the follow-up visits up to day 52 (participants with candidaemia alone in the STRIVE study) and day 59 (all other participants in the STRIVE and ReSTORE studies). From the pooled population, 64 subjects died according to the information subsequently submitted in the written statement procedure, 30 of them in the intervention arms and 34 in the control arms. However, it is unclear which data cut-offs were used for the evaluation. The pharmaceutical company does not provide effect estimators for the results at the pre-specified data cut-off. According to the final study report, 22 subjects had died in the caspofungin arm of the ReSTORE study at follow-up; 24 deaths were recorded in the subsequently submitted documents. The pharmaceutical company did not give any justification for this deviation. Due to the uncertainties in the collection of the endpoint, the endpoint of overall mortality is not used for the benefit assessment and is only presented additionally. The data presented did not show any significant differences between the study arms.

Morbidity

Global cure

"Global cure" is a composite endpoint consisting of the components clinical, mycological and radiological (in subjects with invasive candidiasis) response. In the ReSTORE study, the assessment was based on the principal investigator's estimate at all data collection time points and had to be confirmed by an independent, blinded Data Review Committee (DRC). The "global cure" endpoint was classified as unfulfilled (failure) if one of these three individual components was not given or remained undetermined. This endpoint was not collected in the STRIVE study.

"Global cure on day 14" is the primary endpoint for the EMA in the ReSTORE study.

The patient relevance of the "mycological eradication" subcomponent is unclear. The suitability of the "clinical response" endpoint also remains unclear due to considerable uncertainties in the operationalisation. (see below for further information on the operationalisation and patient relevance of these two endpoints).

Radiological cure is not immediately noticeable for patients. However, the first two components, which are at least partially noticeable to patients and relevant for therapy management, predominate since radiological cure cannot determine the success of the "global cure" endpoint without a simultaneous clinical and mycological response. The "global cure" composite endpoint is only presented additionally due to the unclear patient relevance of the "mycological eradication" subcomponent and considerable uncertainties in the operationalisation of the "clinical response" endpoint. The evaluations do not show any significant differences between the study arms.

Overall response

"Overall response on day 14" is the primary efficacy endpoint of the STRIVE study. This is a composite endpoint whose assessment as "success" is made up of the components "mycological eradication" and "remission of systemic signs and symptoms". The assessment was carried out by the principal investigator at all survey time points with the exception of the visit at the end of treatment; the overall response on day 5, day 28 and at the final follow-up visit were defined as secondary endpoints in the STRIVE study.

The patient relevance of the "mycological eradication" subcomponent is unclear. The suitability of the "remission of attributable systemic signs and symptoms" endpoint also remains unclear due to considerable uncertainties in the operationalisation. (see below for further information on the operationalisation and patient relevance of these two endpoints).

Therefore, the patient relevance of the "overall response on day 14" endpoint is also classified as unclear and it is presented additionally. Irrespective of the uncertainties in the operationalisation, there were no statistically significant differences between the treatment arms in the evaluation.

Mycological eradication

The "mycological eradication" endpoint is a composite endpoint consisting of the components "Candida-negative blood culture/ candida-negative culture from normally sterile body sites", "need for treatment with further antifungal agents" and "survival". The endpoint is a component of the composite endpoints "global cure" (ReSTORE study) and "overall response" (STRIVE study).

The endpoint is crucially based on the laboratory parameter of negative blood culture. The patient relevance is assessed as unclear, as it was not demonstrated to what extent a

documented or presumed mycological eradication is a reliable criterion for a long-term and sustained therapeutic effect. The results of the endpoint are presented additionally as individual components of the composite primary endpoints; they do not show any significant differences between the study arms.

Remission of systemic signs and symptoms

In the ReSTORE and STRIVE studies, the remission of systemic signs and symptoms was considered to be fulfilled at a survey time point if the signs and symptoms attributable to candidaemia and/or invasive candidiasis present at baseline had completely subsided and no new attributable systemic signs and symptoms that were not present at the start of the study had occurred. The signs and symptoms were assessed by the principal investigators. The endpoint was analysed in binary form ("fulfilled" vs "unfulfilled"). Systemic signs attributable to candidiasis included fever, hypothermia, hypotension, tachycardia and tachypnoea according to the study protocol and study report of both studies. In the ReSTORE study, local signs of inflammation (erythema, oedema, heat and pain at the infection site) were also taken into account. The STRIVE study also included the symptoms of fatigue, pain and myalgia.

The remission of relevant systemic signs and symptoms is generally assessed as patient-relevant.

However, there are no operationalisations for the symptoms "pain", "fatigue" and "myalgia". It is therefore unclear how these were collected, e.g. by means of a survey or survey instruments.

Further uncertainties arise from the evaluations submitted by the pharmaceutical company. While in the primary endpoints patients for whom no data were available at the respective survey time point were categorised as non-responders, the evaluations presented by the pharmaceutical company for this endpoint only included the results of study participants for whom data were available at the survey time point. As a result, only a few results were used for evaluations. For this reason, separate calculations on the percentage of responders in relation to the mITT population and corresponding effect estimators were calculated as part of the benefit assessment. In addition, the binary evaluation of the endpoint represents further uncertainty.

The evaluations relating to the miTT population show no significant differences between the study arms on day 14 and at the time of the follow-up. The advantage of rezafungin - claimed by the pharmaceutical company on day 14 - could not be confirmed, irrespective of the unclear suitability of the endpoint for the benefit assessment. The results are presented additionally.

Clinical response

The "clinical response" is a composite endpoint consisting of the components "remission of systemic signs and symptoms", "need for treatment with further antifungal agents" and "survival". The assessment was carried out on the basis of the principal investigator's estimate at all survey time points. The significance of a new systemic antimycotic therapy for patients is to be considered relevant in this therapeutic indication.

However, the suitability of the "remission of systemic signs and symptoms" subcomponent was classified as unclear due to uncertainties in the operationalisation (see above). Therefore, the relevance of the "clinical response" endpoint is also classified as unclear and it is only presented additionally. There were no statistically significant differences between the study arms.

Length of stay in the hospital and the intensive care unit

The number of days in a hospital and the number of days in an intensive care unit were totalled across all stays during the above-mentioned period. The "length of stay in the hospital and the intensive care unit" endpoint is considered patient-relevant. Subjects who died during their stay in the hospital/ intensive care unit were not included in the evaluation. This leads to a selection of the analysed sample and limits the validity of this endpoint. The risk of bias is estimated as high at endpoint level. Nevertheless, the endpoint is used for the benefit assessment, as the operationalisation is considered sufficiently adequate.

Due to the differences in the median observation period between the two studies, which is directly reflected in the survey of hospital days, the results of the individual studies are presented, but not the pooled results. In both studies, there were no statistically significant differences between the study arms.

Quality of life

No data on health-related quality of life were collected.

Side effects

Adverse events (AEs) and serious adverse events (SAEs) were collected continuously during the course of the study.

As there are no additional evaluations that do not take disease-related events into account, it cannot be ruled out that events related to the underlying disease were included in the collection of AEs.

Overall assessment/ conclusion

The results of the pivotal ReSTORE study and the supportive STRIVE study are available for the present benefit assessment for the treatment of invasive candidiasis in adults. The studies compared the safety and efficacy of rezafungin with caspofungin. The treatment phase in both studies lasted between 14 and 28 days; the last visit took place between day 52 and day 59 (ReSTORE) or between day 45 and day 59. Results from the categories of mortality, morbidity and side effects are available.

In the endpoint category of mortality, the endpoint of overall survival is not used for the benefit assessment due to existing uncertainties in the survey. In the additionally presented data, there were no statistically significant differences between the treatment arms.

In the endpoint category of morbidity, the endpoints of length of stay in the hospital and the intensive care unit were used for the benefit assessment. The results did not show any statistically significant differences between the treatment groups.

With regard to side effects, the results did not show any statistically significant differences between the treatment arms.

In the overall assessment of the available results on the patient-relevant endpoints, the G-BA classifies the extent of the additional benefit of rezafungin for the treatment of adults with invasive candidiasis on the basis of the criteria in Section 5, paragraph 8 sentences 1, 2 in conjunction with Section 5, paragraph 7, sentence 1, number 4 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) as non-quantifiable since the scientific data does not allow quantification.

Significance of the evidence

The risk of bias of the ReSTORE and STRIVE studies at study level is estimated to be low.

There are uncertainties regarding the "overall mortality" endpoint, as it is unclear which data cut-offs were used for the evaluation. There is a selection bias in the collection of "length of stay in the hospital and the intensive care unit" due to the exclusion of those who deceased during hospitalisation. Sensitivity analyses were not presented.

In the overall assessment, the significance of the evidence is classified as a hint.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Rezzayo with the active ingredient rezafungin. Rezzayo was approved as an orphan drug.

Rezafungin is indicated for the treatment of invasive candidiasis in adults. The pharmaceutical company submits the RCTs ReSTORE and STRIVE, in which rezafungin was compared with caspofungin.

In the endpoint category of mortality, the endpoint of overall survival was not used for the benefit assessment due to uncertainties in the survey. In the additionally presented data, there were no statistically significant differences between the study arms.

In the endpoint category of morbidity, there were no statistically significant differences between the comparator arms in the "length of stay in the hospital and the intensive care unit" endpoints.

Neither advantages nor disadvantages of rezafungin could be observed for the side effects. No data are available for the endpoint category of health-related quality of life.

In the overall assessment, a hint for a non-quantifiable additional benefit is identified for rezafungin for the treatment of adults with invasive candidiasis since the scientific data does not allow quantification.

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 of the pharmaceutical company. However, the patient numbers estimated by the pharmaceutical company is subject to uncertainty, partly because the ICD-10-GM code B37.1 also includes suspected diagnoses that may not represent confirmed invasive candidiasis. Taken together, an overestimate can be assumed.

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 Rezzayo (active ingredient: rezafungin) agreed upon in the

context of the marketing authorisation at the following publicly accessible link (last access: 29 February 2024):

https://www.ema.europa.eu/en/documents/product-information/rezzayo-epar-product-information_en.pdf

Treatment with rezafungin should only be initiated and monitored by doctors experienced in therapy of invasive fungal infections.

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 July 2024).

The duration of treatment with rezafungin should be based on the patient's clinical and microbiological response in accordance with the product information. In general, antifungal therapy should be continued for at least 14 days after the last positive culture result. During clinical studies, patients were treated with rezafungin for up to 28 days. The safety information on treatment with rezafungin over more than 4 weeks is limited. For the cost calculation, a period of 14 days (minimum treatment duration after positive culture result) and 28 days (maximum treatment duration achieved in studies) is used for the treatment of an infection. The actual treatment duration may vary from patient to patient and may be longer than 28 days.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ infection	Treatment duration/ treatment (days)	Treatment days/ patient/ Infection
Medicinal product to be assessed				
Rezafungin	1 x every 7 days	2.0 - 4.0	1 1	2.0 - 4.0

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ Infection	Average consumption by potency/ infection
Medicinal product to be assessed					
Rezafungin	400 mg on day 1, followed by 200 mg	400 mg on day 1, followed by 200 mg	2 x 200 mg on day 1, followed by 1 x 200 mg	2.0 - 4.0	3.0 x 200 mg - 5.0 x 200 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 Section 130 and Section 130a SGB V. 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 after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the 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					
Rezafungin 200 mg	1 PCI	€ 3,044.69	€ 2.00	€ 170.59	€ 2,872.10
Abbreviations: PCI = powder for a concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 15 July 2024

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 1.10.2009 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 currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. 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.

2.5 Designation of 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 the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates 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.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA 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 G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Adults with invasive candidiasis

- No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

Product information for rezafungin (Rezzayo); REZZAYO 200 mg powder for a concentrate for the preparation of an infusion solution; last revised: December 2023

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 31 January 2024, the pharmaceutical company submitted a dossier for the benefit assessment of rezafungin to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 2 May 2024 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 23 May 2024.

The oral hearing was held on 10 June 2024.

An amendment to the benefit assessment with a supplementary assessment (here only if aspects actually submitted in written statement were reassessed: from data submitted in the written statement procedure) was submitted on 26 June 2024.

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 23 July 2024, and the proposed draft resolution was approved.

At its session on 1 August 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	23 April 2024	Information of the benefit assessment of the G-BA
Working group Section 35a	4 June 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	23 July 2024	Conduct of the oral hearing
Working group Section 35a	18 June 2024 3 July 2024 17 July 2024	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	23 July 2024	Concluding discussion of the draft resolution
Plenum	1 August 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 1 August 2024

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

Prof. Hecken