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 Isavuconazole (new therapeutic indication: aspergillosis, ≥ 1 to ≤ 17 years)

of 20 March 2025

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 all 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 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, 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 active ingredient isavuconazole (Cresemba) was listed for the first time on 15 November 2015 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 22 August 2024, isavuconazole 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 17 September 2024, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 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 active ingredient isavuconazole with the new therapeutic indication "CRESEMBA is indicated in children and adolescents from 1 year of age and older for the treatment of invasive aspergillosis" in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

Isavuconazole for the treatment of invasive aspergillosis 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 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 assess 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 January 2025 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 assessment carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G24-24) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

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 isavuconazole.

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:

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Isavuconazole (Cresemba) in accordance with the product information

CRESEMBA is indicated in patients from 1 year of age and older for the treatment of

- invasive aspergillosis
- mucormycosis in patients for whom amphotericin B is inappropriate.

Therapeutic indication of the resolution (resolution of 20 March 2025):

CRESEMBA is indicated in children and adolescents from 1 year of age and older for the treatment of invasive aspergillosis.

2.1.2 Extent of the additional benefit and significance of the evidence

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

For children and adolescents aged 1 to ≤ 17 years with invasive aspergillosis, there is a hint for a non-quantifiable additional benefit, since the scientific data does not allow quantification.

Justification:

The assessment of isavuconazole in this therapeutic indication is based on the pivotal phase II 9766-CL-0107 study.

The 9766-CL-0107 study is a single-arm, open-label, multicentre phase II study to investigate the safety, pharmacokinetics and efficacy of isavuconazole in children and adolescents aged 1 to ≤ 17 years with invasive aspergillosis or mucormycosis. The sub-population of subjects with invasive aspergillosis is particularly relevant for the present benefit assessment.

31 patients aged 1 to ≤ 17 years who had a proven, probable or possible invasive fungal disease according to the EORTC/MSG criteria of 2008 were enrolled in the study. To be classified as a possible invasive fungal disease, a clinical sign (lower respiratory tract disease, sino-nasal infection, CNS infection) and a host factor (especially immunosuppression) had to be present. The invasive fungal disease had to be classified as probable or proven by diagnostic tests within 10 calendar days after the first administration of the study medication. In addition to clinical signs and the presence of host factors, evidence of a mycological criterion (cytological, microscopic evidence or pathogen culture of a non-sterile sample or galactomannan test) was

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

required to confirm a probable invasive fungal disease. In the case of proven fungal infections, traces of fungal residues were detected in the diseased tissue or blood. In the study analysis, no distinction was made between proven and probable invasive aspergillosis.

Taken together, the population with probable or proven aspergillosis is particularly relevant for the present benefit assessment (N=12). The population with possible invasive fungal disease (N=16) is also considered in order to take into account the conditions in everyday clinical practice, which regularly require immediate initiation of therapy without specific pathogen detection. These patients are also exposed to the potential risks of antifungal therapy. In addition, treatment with isavuconazole may also have a benefit for this patient group if it was not possible to detect a mycological criterion or the fungal pathogen despite the presence of aspergillosis or mucormycosis. Moreover, the study included two participants, who were found to have an invasive fungal disease other than aspergillosis or mucormycosis, and one subject with proven or probable mucormycosis. These patients are not considered in this resolution.

The maximum treatment duration intended for invasive aspergillosis according to the study protocol was 84 days in the 9766-CL-0107 study. The actual treatment duration could be different and even longer. The median treatment duration was 49.5 days (2 - 99) for proven or probable invasive aspergillosis and 69.0 days (6 - 181) for possible invasive fungal disease. After the end of treatment, a follow-up was scheduled for day 30 and day 60 (± 7).

Mortality

The primary endpoint of the study was overall mortality up to day 42. By day 42, two subjects had died, one with proven or probable invasive aspergillosis and one with possible invasive fungal disease.

Morbidity

Morbidity was assessed in the 9766-CL-0107 study via the secondary efficacy endpoint components of clinical, radiological and mycological response as well as the efficacy endpoint of overall response, which was composed of the aforementioned individual components.

Overall response

"Overall response" is a composite endpoint consisting of the components "clinical response", "mycological response" and "radiological response". The documentation of clinical, mycological and radiological assessments, tests and procedures for the assessment of the individual components was carried out continuously throughout the entire treatment duration, but only until the end of treatment (EOT).

The "overall response" was rated to be a "success" if all 3 individual components were rated as successful (see below for a detailed description of the operationalisation and success criteria of the individual components). A distinction was made between "complete success" and "partial success", whereby the study documents do not contain any further specification of the "partial success" category. "Failure" was present in case of stability of the individual components or progression. If one of the individual components was not analysed, the overall response was classified as "not analysable".

The patient relevance of the subcomponents "mycological response" and "radiological response" is unclear (see below). The validity of the "clinical response" endpoint is assessed as unclear (see below). The "overall response" endpoint is therefore not used for the benefit assessment.

Clinical response

The "clinical response" endpoint as an individual component of the "overall response" composite endpoint includes the complete or partial remission of infection-related signs and symptoms and physical findings (successful clinical response). These included signs and symptoms such as fever, dyspnoea, haemoptysis, productive and non-productive cough, nasal discharge, pleural pain, pleural rub and erythematous papules or nodules. Failure for this endpoint was defined as no or little change, deterioration or recurrence of signs, symptoms or findings, or the need for alternative systemic antifungal therapy.

An assessment of the severity grade or assessment of the improvement/ deterioration of the symptomatology/ findings was not carried out. The clinical response was assessed by the principal investigator and the Adjudication Committee (AC) based on the documentation of symptoms, signs and physical findings by the principal investigators. The "clinical response according to the principal investigators" endpoint assumes greater significance than the "clinical response according to the AC" endpoint as the AC had no direct contact with the patients. The endpoint was analysed for the time points EOT, day 42 and day 84, but not beyond the EOT.

The remission of relevant systemic signs and symptoms is generally assessed as patient-relevant. However, the validity of the "clinical response" endpoint in the operationalisation presented is assessed as unclear. There are uncertainties regarding the collection and documentation of symptoms and findings as well as the categorisation as "infection-related". It is not clear which physical findings and medical and surgical interventions should be included in the endpoint. Furthermore, the "success" category, which also included the partial remission of at least some infection-related symptoms and physical findings ("partial success"), cannot be clearly distinguished from the "failure" category, which also included "minor" changes. A differentiation between the remission of some (partial success) and all infection-related signs and symptoms (complete success) was not made in the submitted evaluation. The significance of the survey is also questionable in view of the high rates of further antifungal therapies during the course of the study (IA: 7 (58.3%), possible fungal disease: 10 (62.5%)).

Since the morbidity endpoints were only assessed up to the EOT, major variance in the actual treatment duration (2 to 99 days), and thus at the time of observation, must also be taken into account in the evaluation.

Due to major uncertainties in validity, the data on the "clinical response" endpoint is not assessable overall and are therefore not used for the benefit assessment.

Mycological response

Success in mycological response was defined as a (presumed) elimination of the pathogen and is a subcomponent of the "overall response" endpoint, proven by microbiological tests.

The endpoint is based on microbiological laboratory parameters. 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 "mycological response" endpoint is therefore not used for the benefit assessment.

Radiological response

Imaging procedures (depending on the infected body region, e.g. MRI or CT) should be used throughout the course of the study for follow-up diagnostics. The radiological response was assessed by both the principal investigator and the AC.

A radiological cure is not immediately noticeable for the patients and is therefore not patient-relevant per se. There are also ambiguities in the survey. The type and frequency of imaging procedures used is not described in the 9766-CL-0107 study, which is why it is unclear which imaging evidence was used for assessment of the radiological response. The "radiological response" endpoint is therefore not used for the benefit assessment.

Quality of life

No health-related quality of life data were collected in the 9766-CL-0107 study.

Side effects

Adverse events (AEs) and serious adverse events (SAEs) were collected from the signing of the informed consent form until 60 days after EOT. The operationalisation is considered valid. Due to the single-arm study design, no statement on the extent of additional benefit can be derived from the data.

Overall assessment

The results of the pivotal, single-arm, open-label, multicentre phase II 9766-CL-0107 study to investigate the safety, pharmacokinetics and efficacy of isavuconazole in children and adolescents aged 1 to ≤ 17 years with invasive aspergillosis or mucormycosis are available for the present benefit assessment for the treatment of invasive aspergillosis in children and adolescents aged 1 year and older. The sub-population of subjects with invasive aspergillosis is particularly relevant for the present benefit assessment.

The median treatment duration was 49.5 days (2 - 99) for proven or probable invasive aspergillosis and 69.0 days (6 - 181) for possible invasive fungal disease. After the end of treatment, a follow-up was scheduled for day 30 and day 60 (± 7). Results from the categories of mortality, morbidity and side effects are available.

The primary endpoint of the study was overall mortality up to day 42. By day 42, two subjects had died.

In the endpoint category of morbidity, the endpoint components of clinical, radiological and mycological response as well as the overall response composed of the aforementioned individual components were assessed. Due to existing uncertainties regarding patient relevance and/or validity in the survey, none of these endpoints could be used for the benefit assessment.

Due to the single-arm study design, no statements on the extent of the additional benefit of isavuconazole can be derived from the data on mortality and side effects.

In the overall assessment, the G-BA classifies the extent of the additional benefit as non-quantifiable since the scientific data does not allow quantification.

Significance of the evidence

The present assessment is based on the results of the open-label, uncontrolled phase II 9766-CL-0107 study. The risk of bias is assessed as high both at study level and at endpoint level due to the open-label study design. The significance of the evidence is therefore classified in the "hint" category.

2.1.3 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient isavuconazole. Cresemba was approved as an orphan drug. The therapeutic indication assessed here is as follows: "CRESEMBA is indicated in children and adolescents from 1 year of age and older for the treatment of invasive aspergillosis."

For the benefit assessment, the pharmaceutical company presented the single-arm, open-label, multicentre phase II 9766-CL-0107 study to investigate the safety, pharmacokinetics and efficacy of isavuconazole in children and adolescents aged 1 to ≤ 17 years with invasive aspergillosis or mucormycosis.

No statements on the extent of the additional benefit can be derived on the basis of the study results presented due to the single-arm study design of the 9766-CL-0107 study.

In the overall assessment, there is therefore a hint for a non-quantifiable additional benefit of isovuconazole in the therapeutic indication "invasive aspergillosis in children and adolescents aged 1 to ≤ 17 years" since the scientific data basis 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. Although the patient numbers estimated by the pharmaceutical company is subject to uncertainty, it can be assumed that the total number of children and adolescents aged 1 to ≤ 17 years with invasive aspergillosis is within the stated range.

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 Cresemba (active ingredient: isavuconazole) at the following publicly accessible link (last access: 10 February 2025):

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

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 March 2025).

According to the product information, the duration of treatment should be determined according to the clinical response. For long-term treatments over a period of more than 6 months, the benefit-risk ratio should be carefully weighed up.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. 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.

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				
Isavuconazole	Continuously, 1 x daily[2]	365	1	365

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 co-morbidities) are not taken into account when calculating the annual treatment costs.

The active ingredient isavuconazole is dosed in children and adolescents according to body weight. The cost calculation is based on an average body weight of 11.6 kg for patients between 1 and 2 years of age[3] and 67.2 kg for patients between 17 and 18 years of age [4].

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

[2] not taking into account the loading dose (every 8 hours in the first 48 hours)

[3] Federal Health Reporting. Average body measurements of the population (2017, both sexes, 1 year and older), www.gbe-bund.de

[4] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

Isavuconazole is available in both intravenous and oral dosage forms; switching between dosage forms is possible if clinically indicated.

Isavuconazole hard capsules are only indicated for the age of 6 years and above. The 40 mg hard capsules are intended for use in children and adolescents. However, these are not yet sold in Germany. Children and adolescents between 6 and 18 years of age with a body weight of at least 32 kg can receive 100 mg hard capsules according to the product information - but the use has not been investigated in children and adolescents.

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					
Isavuconazole Body weight < 37 kg	5.4 mg/kg -	62.6 mg -	1 x 100 mg -	365	365 x 100 mg -
Body weight ≥ 37 kg	200 mg	200 mg	2 x 100 mg	365	730 x 100 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.

Isavuconazole as solution for infusion 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.

Costs of the medicinal products:

Children and adolescents aged 1 to ≤ 17 years with invasive aspergillosis

Designation of the therapy	Packaging size	Packaging size Costs (clinic purchase registry)	Value added tax (19%)		Costs of the medicinal product
Medicinal product to be assessed					
Isavuconazole 100 mg	1 PIC	€ 380.00	€ 72.20		€ 452.20

	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Isavuconazole 100 mg	14 HC	€ 928.14	€ 1.77	€ 50.76	€ 875.61
Abbreviations: HC = hard capsules; PIC = powder for the preparation of an infusion solution concentrate					

LAUER-TAXE® last revised: 1 March 2025

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.

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 requirements 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:

Children and adolescents aged 1 to ≤ 17 years with invasive aspergillosis

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

References:
Product information for isavuconazole (Cresemba); Cresemba 40 mg hard capsules Cresemba 100 mg hard capsules; last revised: August 2024

Product information for isavuconazole (Cresemba); CRESEMBA 200 mg powder for a concentrate for the preparation of an infusion solution; last revised: August 2024

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

The benefit assessment of the G-BA was published on 2 January 2025 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 January 2025.

The oral hearing was held on 10 February 2025.

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 11 March 2025, and the draft resolution was approved.

At its session on 20 March 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	17 December 2024	Information of the benefit assessment of the G-BA
Working group Section 35a	5 February 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	10 February 2025	Conduct of the oral hearing
Working group Section 35a	19 February 2025 5 March 2025	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 on Medicinal Products	11 March 2025	Concluding discussion of the draft resolution
Plenum	20 March 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 20 March 2025

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

Prof. Hecken