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
Artesunate (severe malaria, from birth)

of 17 April 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, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at their 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 their 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 artesunate for the initial treatment of severe malaria in adults and children 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 medical benefit is thus 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). According to Section 5 paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified, stating the significance of the evidence.

The relevant date for the start of the benefit assessment procedure is the first placing on the (German) market of the active ingredient in accordance with Section 4, paragraph 3, number 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. For the active ingredient artesunate, this took place on 1 November 2024. The pharmaceutical company did not submit any benefit assessment dossier at the relevant time. Consequently, the required evidence for the benefit assessment according to Section 35a SGB V was not submitted to the G-BA.

According to Section 5, paragraph 8, sentence 2 in conjunction with paragraph 7, sentence 1, number 4 AM-NutzenV, a non-quantifiable additional benefit therefore results since the required evidence is incomplete.

The G-BA has prepared a benefit assessment including treatment costs and patient numbers. The benefit assessment was published on 3 February 2025 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure.

In addition, an oral hearing was held.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Artesunate (Artesunate Amivas) in accordance with the product information

Artesunate Amivas is indicated for the initial treatment of severe malaria in adults and children. Consideration should be given to official guidelines on the appropriate use of antimalarial agents.

Therapeutic indication of the resolution (resolution of 17 April 2025):

See the approved therapeutic indication.

2.1.2 Extent of the additional benefit and significance of the evidence

In summary, the additional benefit of artesunate is assessed as follows:
The pharmaceutical company did not submit any benefit assessment dossier for the active ingredient artesunate. Thus, the required evidence for the benefit assessment according to Section 35a SGB V was not submitted to the G-BA.

According to Section 5, paragraph 8, sentence 2 in conjunction with paragraph 7, sentence 1, number 4 AM-NutzenV, a non-quantifiable additional benefit therefore results since the required provision of evidence is incomplete.

2.1.3 Summary of the assessment

This assessment concerns the benefit assessment for the active ingredient artesunate in the therapeutic indication:

"Artesunate Amivas is indicated for the initial treatment of severe malaria in adults and children."

Artesunate for the initial treatment of severe malaria in adults and children 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.

The pharmaceutical company did not submit any benefit assessment dossier at the relevant time. Thus, the required evidence for the benefit assessment according to Section 35a SGB V was not submitted to the G-BA.

According to Section 5, paragraph 8, sentence 2 in conjunction with paragraph 7, sentence 1, number 4 AM-NutzenV, a non-quantifiable additional benefit of the active ingredient artesunate therefore results since the required evidence is incomplete.

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.

The reporting data under the Infection Protection Act (IfSG), transmitted to the Robert Koch Institute (RKI) as of 15 May 2024[1], was used to calculate the number of patients with malaria in Germany. This shows that a total of 985 malaria cases were reported in 2023 (laboratory detection by microscopy, nucleic acid detection or antigen test; for reports in accordance with Section 7 paragraph 3 IfSG, the main residence of the case is also not abroad). Information on the pathogen species was available in 886 cases (90% of all cases). The percentage of infections with the pathogen *Plasmodium falciparum,* which is the main cause of the severe form of malaria, was 84.4% in 2023.

However, the percentage of severe malaria cases in Europe is only 10% of the total number of malaria infections when taking into account the information in the European Public Assessment Report (EPAR)[2] for artesunate. Assuming that this is also transferable to Germany, this results in around 99 patients who are eligible for treatment with artesunate - in deviation from the number of patients presented in the benefit assessment. However, this figure is subject to certain uncertainties, as only pan-European data is available for the percentage of severe malaria cases, not specific data for Germany. Taking into account the percentage of patients with statutory health insurance, this results in a total of around 87 patients.

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 Artesunate Amivas (active ingredient: artesunate) at the following publicly accessible link (last access: 7 November 2024):

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

Treatment with artesunate should only be initiated and monitored by doctors experienced in severe malaria therapy.

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 April 2025).

Treatment period:

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

Artesunate Amivas is administered by intravenous injection (24 mg/kg body weight (BW)) after 0, 12 and 24 hours in accordance with the requirements in the product information. After at least 24 hours (3 doses) of treatment with Artesunate Amivas, patients who are intolerant

[1] Epidemiological Bulletin (issue 45, 2024) of the Robert Koch Institute (as of 07.11.2024)
[2] https://www.ema.europa.eu/en/documents/assessment-report/artesunate-amivas-epar-public-assessment-report_en.pdf

to oral treatment can continue intravenous treatment with 2.4 mg/kg BW once every 24 hours (48 hours after the start of treatment). Actual consumption may therefore be different from patient to patient and may exceed 3 doses.

Treatment with Artesunate Amivas should be discontinued as soon as patients are tolerant to oral treatment. After discontinuation of Artesunate Amivas, all patients should receive a full course of treatment with a suitable oral combination regimen for the treatment of malaria.

Children (from birth) and adults with severe malaria (for initial treatment)

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Artesunate	Every 12 hours (at least 3 treatments)	1	1	1

Consumption:

The average body measurements were applied for dosages depending on body weight (BW) or body surface area (BSA) (average body weight of a child postnatal: 3.46 kg[3], average body weight of an adult 18 years and older: 77.7 kg[4]).

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 consumption is presented for the medicinal product to be assessed, Artesunate Amivas, according to the requirements in the product information.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Artesunate					
Children (newborns)	2.4 mg/kg	3 x 8.3 mg = 24.9 mg	3 x 110 mg	1	3 x 110 mg
Adults (18 years and older)	2.4 mg/kg	3 x 186.5 mg = 559.4 mg	6 x 110 mg	1	6 x 110 mg

[3] Reference percentiles for anthropometric measures and blood pressure from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS), 2. updated 2013 edition

[4] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 18 years and older), www.gbe-bund.de

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Costs:

Artesunate Amivas is listed in LAUER-TAXE® as a clinic pack only. 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.

Costs of the medicinal products:

Children (from birth) and adults with severe malaria (for initial treatment)

Designation of the therapy	Packaging size	Costs (purchase price of clinic pack plus value added tax)	Value added tax (19%)	Costs of the medicinal product
Medicinal product to be assessed				
Artesunate 110 mg	2 PSI	€ 3,200	€ 608	€ 3,808
Abbreviations: PSI = powder and solvent for solution for injection				

LAUER-TAXE® last revised: 1 April 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 (from birth) and adults with severe malaria (for initial treatment)

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 artesunate (Artesunate Amivas); Artesunate Amivas 110 mg powder and solvent for solution for injection; last revised: April 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

The pharmaceutical company did not submit a dossier for the benefit assessment of artesunate at the relevant time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO to the G-BA.

The benefit assessment of the G-BA was published on 3 February 2025 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 24 February 2025.

The oral hearing was held on 10 March 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 8 April 2025, and the proposed draft resolution was approved.

At their session on 17 April 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	28 January 2025	Information of the benefit assessment of the G-BA
Working group Section 35a	4 March 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	10 March 2025	Conduct of the oral hearing
Working group Section 35a	19 March 2025 2 April 2025	Consultation on the dossier evaluation by the G-BA and evaluation of the written statement procedure
Subcommittee on Medicinal Products	8 April 2025	Concluding discussion of the draft resolution
Plenum	17 April 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 17 April 2025

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

Prof. Hecken