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)
Enalapril (heart failure, from birth to ≤ 17 years)

of 15 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 all reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment 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 enalapril is considered a new active ingredient within the meaning of Section 35a paragraph 1 SGB V in conjunction with Chapter 5 Section 2, paragraph 1, sentence 3, number 2 of the G-BA's Rules of Procedure (VerfO), as it has been granted a marketing authorisation for paediatric use in accordance with Articles 5 to 15 of Regulation (EC) No. 726/2004 pursuant to Article 38 paragraph 1 of Regulation (EC) No. 1901/2006 - Regulation on medicinal products for paediatric use.

The relevant date for the first placing on the (German) market of the medicinal product Aqumeldi with the active ingredient enalapril in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO is 1 March 2024. The pharmaceutical company submitted the final dossier in due time 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 29 February 2024.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 3 June 2024 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of enalapril compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment 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 data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods[1] was not used in the benefit assessment of enalapril.

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 in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Enalapril (Aqumeldi) in accordance with the product information

AQUMELDI is indicated for the treatment of heart failure in children from birth to less than 18 years.

Therapeutic indication of the resolution (resolution of 15 August 2024):

See the approved therapeutic indication.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Children and adolescents from 1 to ≤ 17 years of age with heart failure

Appropriate comparator therapy for enalapril:

- Captopril or sacubitril/ valsartan

b) Children from birth to < 1 year of age with heart failure

Appropriate comparator therapy for enalapril:

- Captopril

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

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

on 1. According to the statements of the scientific-medical societies and clinical experts and on the basis of the inclusion criteria of the approval studies of enalapril, it must be

assumed that children and adolescents with chronic heart failure who have left ventricular dysfunction are considered in the present therapeutic indication.

In addition to enalapril, the ACE inhibitor captopril, the fixed combination of an ARB[2] and ARNI[3] sacubitril/valsartan, as well as digitalis glycosides are approved for the treatment of infants, children and adolescents with chronic heart failure and left ventricular dysfunction.

on 2. Non-medicinal treatment options are not considered in the present therapeutic indication as a rule.

on 3. The following resolution of the G-BA on the early benefit assessment of medicinal products with new active ingredients is available for this therapeutic indication in children and adolescents with chronic heart failure (Annex XII to the Pharmaceuticals Directive):

- Sacubitril/valsartan of 7 December 2023.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication.

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

The available evidence on the treatment of children and adolescents with symptomatic chronic heart failure is limited overall. The German S2k guideline "Chronic heart failure in childhood and adolescence"[4] has not been updated for more than 5 years and is currently being revised. The statements in the aforementioned guideline and the opinions of the scientific-medical societies are congruent with the fact that the guideline-based therapy options for adults with chronic heart failure are generally adopted for the treatment of children and adolescents in this therapeutic indication.

For the treatment of chronic heart failure in adults, ACE inhibitors (ACEi), AT1 receptor blockers, ARNI, beta receptor blockers, SGLT-2 inhibitors and MRA[5] are prognosis-improving substance groups. If adults with heart failure and reduced ejection fraction are not yet receiving all prognosis-improving substances and are still symptomatic, further intensification of therapy, including diuretics, should be recommended, taking into account individual therapy goals, comorbidity and tolerability.

According to the guideline,[6] there is evidence with moderate reliability of data for the use of ARNI *(sacubitril/valsartan)* in adults who have been pretreated with ACEi/ARB and are still symptomatic. For adults not pretreated with ACEi/ARB and/or with *de novo* heart failure, the reliability of data is low. In summary, the guideline recommends the

[2] ARB = AT1 receptor blocker
[3] ARNI = angiotensin receptor neprilysin inhibitor
[4] AWMF register number 023/006 last revised 31.10.2015, valid until 30.10.2020
[5] MRA = mineralocorticoid receptor antagonists
[6] National Care Guideline Chronic Heart Failure - long version. Version 4.0. 2023 *[accessed 18.07.2024]* DOI: 10.6101/AZQ/000510. https://www.leitlinien.de/themen/herzinsuffizienz

use of sacubitril/valsartan in adults with persistent symptomatology under basic therapy with ACEi/ARB or, if necessary, also initially.

Digitalis glycosides can only be recommended to patients in sinus rhythm who remain significantly symptomatic despite guideline-compliant therapy with prognosis-improving active ingredients, dosed according to the target plasma concentration.

Overall, the treatment recommendations regarding the off-label use of medicinal products of the above-mentioned product classes in the paediatric patient population are merely consensus-based recommendations based on the findings of heart failure in adults. Accordingly, there is a lack of sufficient evidence for paediatric heart failure to justify the current clinical treatment practice in the off-label use in children and adolescents.

Captopril is approved for the treatment of paediatric heart failure and is regularly used in the care of infants, children and adolescents with heart failure.

Sacubitril/valsartan is also approved for use in children from 1 year of age and adolescents in the present therapeutic indication.

In summary, neither high-quality evidence nor valid evidence-based recommendations for the off-label use of the above-mentioned active ingredients or product classes can be derived in the relevant patient population. Thus, according to the generally recognised state of medical knowledge, the off-label use must not be preferred to the medicinal products approved in the therapeutic indication as a rule.

Based on the approved medicinal treatment options for the therapeutic indication two patient populations are distinguished.

Based on the generally recognised state of medical knowledge and taking into account the authorisation status of captopril and sacubitril/ valsartan as well as the available evidence for paediatric heart failure, captopril or sacubitril/valsartan are determined as the appropriate comparator therapy for the patient population a) children 1 year and older and adolescents ≤ 17 years of age.

For the patient population b) infants and children from birth to < 1 year of age, the active ingredient captopril is determined as the appropriate comparator therapy.

If patients have concomitant symptoms of the underlying disease(s) or risk factors such as tachycardia, tachypnoea, oedema, ascites, pain, hypertension or cardiac arrhythmia, patient-individual treatment must be ensured in accordance with the generally recognised state of scientific knowledge.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

a) Children and adolescents from 1 to ≤ 17 years of age with heart failure

An additional benefit is not proven.

b) Children from birth to < 1 year of age with heart failure

An additional benefit is not proven.

Justification:

For the assessment of the additional benefit of enalapril compared with the appropriate comparator therapy for the treatment of heart failure in children from birth to ≤ 17 years of age, the pharmaceutical company presented the single-arm WP08 and WP09 studies and the WP10 extension study. The single-arm studies investigate the pharmacokinetics, pharmacodynamics, acceptability and safety profile of enalapril as an orodispersible tablet.

The WP08 study enrolled 32 children 1 month to < 12 years of age with dilated cardiomyopathy who had heart failure with signs of left ventricular systolic dysfunction. The WP09 study enrolled 70 children from birth to < 6 years of age with heart failure due to a congenital heart defect who required a reduction in afterload by means of medicinal treatment. A total of 86 children were treated in the WP10 extension study.

Due to the single-arm study design, the WP08, WP09 and WP10 studies presented do not allow a comparison of enalapril with the appropriate comparator therapy. For this reason, the studies are unsuitable for deriving conclusions on the additional benefit of enalapril compared with the appropriate comparator therapy.

Exclusion of the PANORAMA-HF study *(comparison of enalapril with sacubitril/ valsartan)*

As part of the information procurement for the assessment of children and adolescents 1 to ≤ 17 years of age with heart failure (patient population a), the pharmaceutical company identified the PANORAMA-HF study for the direct comparison of enalapril with the combination of active ingredients sacubitril/valsartan.[7] This comparison basically corresponds to the implementation of the determined appropriate comparator therapy. However, the pharmaceutical company excludes the PANORAMA-HF study because it does not fulfil the defined selection criterion of an enalapril maintenance dose of 0.15 to 0.3 mg/kg per day.

The pharmaceutical company's approach of excluding the PANORAMA-HF study is considered inappropriate. Although there are deviations between the dosage regimen of enalapril in the PANORAMA-HF study *(0.2 mg/kg per single dose twice daily, maximum 20 mg per day)* and the recommended maintenance dose of enalapril according to the marketing authorisation *(0.15 to 0.3 mg/kg, maximum 20 mg per day)*, this does not justify the exclusion from the study.

[7] For the assessment of the PANORAMA-HF study, cf. the resolution and justification for the early benefit assessment of sacubitril/valsartan in the new therapeutic indication: chronic heart failure with left ventricular dysfunction in the age between 1 and 17 years https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/963/#beschluesse as well as the corresponding IQWiG report (dossier assessment A23-56 and addendum A23-103).

In the PANORAMA-HF study, children and adolescents 1 month to ≤ 17 years of age with chronic heart failure due to left ventricular dysfunction were examined for 52 weeks. The patient population in the PANORAMA-HF study thus corresponds to the target population in the therapeutic indication of enalapril. For the comparison of enalapril with sacubitril/valsartan, enalapril in liquid dosage form was gradually titrated from an starting dose of 0.1 to 0.2 mg/kg in the younger children up to a target dose of 0.4 mg/kg per day. When using enalapril as a tablet, the dose was increased from 5 to 10 mg per day to the target dose of 20 mg per day.

Even if the enalapril dosage regimen in the PANORAMA-HF study deviated slightly from the approved dosage, the enalapril administration overall represents a sufficient approximation of the on-label application. The exclusion of the PANORAMA-HF study is therefore considered inappropriate.

Overall, the pharmaceutical company therefore did not present any data that allow a comparison of enalapril with the appropriate comparator therapy. An additional benefit of enalapril compared to the appropriate comparator therapy is therefore not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Aqumeldi with the active ingredient enalapril.

Enalapril is approved for the treatment of heart failure in children from birth to less than 18 years.

In the therapeutic indication to be considered, 2 patient groups were distinguished.

a) Children and adolescents from 1 to ≤ 17 years of age with heart failure

Captopril or sacubitril/valsartan is determined as the appropriate comparator therapy.

The single-arm WP08 and WP09 studies and the WP10 extension study were presented for the assessment of the additional benefit of enalapril for the treatment of heart failure in children from birth to under 18 years of age. The single-arm studies investigate the pharmacokinetics, pharmacodynamics, acceptability and safety profile of enalapril as an orally disintegrating tablet.

Although the pharmaceutical company identified the PANORAMA-HF study for the direct comparison of enalapril with sacubitril/valsartan, it excluded this study due to minor deviations from the approved doses of enalapril. The exclusion of the PANORAMA-HF study is inappropriate. The administration of enalapril in the study represents a sufficient approximation of an on-label application.

The presented single-arm studies are unsuitable for the benefit assessment due to the lack of comparison with the appropriate comparator therapy. An additional benefit of enalapril compared to the appropriate comparator therapy is therefore not proven.

b) Children from birth to < 1 year of age with heart failure

Captopril was determined to be the appropriate comparator therapy.

The single-arm WP08 and WP09 studies and the WP10 extension study were presented for the assessment of the additional benefit of enalapril for the treatment of heart failure in children from birth to under 18 years of age. The single-arm studies investigate the

pharmacokinetics, pharmacodynamics, acceptability and safety profile of enalapril as an orally disintegrating tablet.

The presented single-arm studies are unsuitable for the benefit assessment due to the lack of comparison with the appropriate comparator therapy. An additional benefit of enalapril compared to the appropriate comparator therapy is therefore not proven.

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 patient numbers stated in the pharmaceutical company's dossier. IQWiG's calculation is taken into account for the information on the number of children and adolescents in the respective patient population.[8]

Based on the statements of the scientific-medical societies and clinical experts as well as the inclusion criteria of the approval studies of enalapril, it is assumed that only children and adolescents with chronic heart failure with left ventricular dysfunction are included in the therapeutic indication for enalapril.

For the classification of patient numbers in the patient population a) children and adolescents from 1 to 17 years of age with heart failure, data on the SHI target population in a similar therapeutic indication are available: Children and adolescents 1 to ≤ 17 years of age with symptomatic, chronic heart failure with left ventricular dysfunction, in the previous assessment procedure for the combination of active ingredients sacubitril/ valsartan from 2023. Compared to the assessment procedure for sacubitril/ valsartan,[9] the specified patient numbers in the patient population a) for enalapril are higher.

Due to various uncertainty factors[8] in determining the patient numbers in the SHI target population of enalapril, the information on the SHI target population is subject to uncertainties overall. The determination of patient numbers in the previous assessment procedure for the combination of active ingredients sacubitril/ valsartan was also subject to uncertainties. Overall, probable underestimation of the SHI target population was therefore 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 Aqumeldi (active ingredient: enalapril) agreed upon in the context of the marketing authorisation at the following publicly accessible link (last access: 8 July 2024):

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

Treatment with enalapril should only be initiated and monitored by doctors experienced in treating children and adolescents with heart failure.

[8] IQWiG's dossier assessment enalapril, heart failure in children and adolescents from 28.05.2024.
[9] IQWiG dossier assessment sacubitril/ valsartan, heart failure in children and adolescents from 31.10.2023.

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).

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.

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied. The average body weight of children below 1 year of age is 7.6 kg, of 1-year-olds 11.6 kg and of 17-year-olds 67.0 kg[10]. The average body weight of 3.46 kg was used for the dosage in relation to the body weight of a newborn. This results from the average body weight of a boy (3.53 kg) and a girl (3.39 kg)[11].

As it is not always possible to achieve the exact calculated dose per day with the commercially available dose potencies, in these cases rounding up or down to the next higher or lower available dose that can be achieved with the commercially available dose potencies as well as the scalability of the respective dosage form.

According to the product information, the target/ maintenance dose of enalapril is 0.15 mg/kg to 0.3 mg/kg (maximum 20 mg) per day. For both patient populations, the lower limit of 0.15 mg/kg is used as the target/ maintenance dose. For patient population a), the maximum dose of 20 mg enalapril represents the upper limit. For patient population b), the target/ maintenance dose of 0.3 mg/kg represents the upper limit.

According to the product information for sacubitril/ valsartan, the film-coated tablets are unsuitable for children weighing less than 40 kg. For this patient group, the granules are used as the basis for calculation. Two dosage forms of the combination medicinal product sacubitril/ valsartan are available for children and adolescents weighing over 40 kg: Granules and film-coated tablets. Since only the film-coated tablets can be used to achieve the exact dosage according to the product information, the film-coated tablets are used to calculate the costs for this patient group.

In this particular patient population, it is up to the physician to decide which is the most appropriate dosage form for the respective child from 1 to < 6 years of age, depending on body weight and dose. For this reason, where available, the dosages of both a solid (film-coated tablet or hard capsule) and a liquid formulation (solution or suspension) are shown for each active ingredient. In the present case, the lowest possible dosage of captopril tablets (6.25 mg per application) is only suitable for 5-year-old children with a body weight of 20.8 kg. According to the product information for captopril, the starting dose for children and adolescents aged 1 year and over is 0.3 mg/kg. For newborns and infants under 1 year of age, the starting dose is 0.15 mg/kg.

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

[11] Contributions to Federal Health Reporting, Robert Koch Institute, Berlin, 2013: Reference percentiles for anthropometric measures and blood pressure from the Study on the Health of Children and Adolescents in Germany [last access 8 July 2024] (KiGGS). https://edoc.rki.de/bitstream/handle/176904/3254/28jWMa04ZjppM.pdf?sequence=1&isAllowed=y

Treatment period:

a) Children and adolescents from 1 to ≤ 17 years of age with heart failure

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Enalapril	Continuously, 1 to 2 x daily	365.0	1	365.0
Appropriate comparator therapy				
Sacubitril/ valsartan	Continuously, 2 x daily	365.0	1	365.0
Captopril	Continuously, 3 x daily	365.0	1	365.0

b) Children from birth to < 1 year of age with heart failure

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Enalapril	Continuously, 1 to 2 x daily	365.0	1	365.0
Appropriate comparator therapy				
Captopril	Continuously, 3 x daily	365.0	1	365.0

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.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

a) Children and adolescents from 1 to ≤ 17 years of age with heart failure

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					
Enalapril ODT	0.15 mg/kg - 0.3 mg/kg ≙ 1.74 mg – 20 mg	1.74 mg – 20 mg	7 x 0.25 mg – 80 x 0.25 mg	365.0	2,555 x 0.25 mg – 29,200 x 0.25 mg
Appropriate comparator therapy					
Sacubitril/ valsartan GRC	Children under 40 kg BW				
	3.1 mg/kg = 36 mg	72 mg	6x 6 mg/6 mg	365.0	2,190.0 x 6 mg/6 mg
Sacubitril/ valsartan FCT	Children above 40 kg BW				
	72 mg/78 mg[12] – 97 mg/103 mg	144 mg/156 mg – 194 mg/206 mg	6 x 24 mg/26 mg – 2 x 97 mg/103 mg	365.0	2,190 x 24 mg/26 mg – 730 x 97 mg/103 mg
Captopril 1-year-olds OS	0.3 mg /kg = 3.5 mg ≙ 3.5 ml	10.5 mg ≙ 10.5 ml	3 x 3.5 ml	365.0	1,095 x 3.5 ml = 3,832.5 ml
Captopril 5-year-olds OS	0.3 mg/kg = 6.2 mg ≙ 6.2 ml	18.6 mg ≙ 18.6 ml	3 x 6.2 ml	365.0	1,095 x 6.2 ml = 6,789 ml
Captopril 5 to 6-year olds TAB	0.3 mg/kg = 6.2 mg - 7.1 mg	18.75 mg	3 x ½ 12.5 mg	365.0	1,095 x ½ 12.5 mg
Captopril 17-year-olds TAB	20.1 mg	56.25 mg	3 x 12.5 mg + 3 x ½ 12.5 mg	365.0	1,095 x 12.5 mg + 1,095 x ½ 12.5 mg
Abbreviations: FCT = film-coated tablets; GRC = granules for release from capsules; OS = oral solution; ODT = orally disintegrating tablets; TAB = tablets					

b) Children from birth to < 1 year of age with heart failure

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					
Enalapril ODT	0.15 mg/kg - 0.3 mg/kg ≙				730 x 0.25 mg -

[12] Dosage for children above 6 years of age with a BW of 23.6 kg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	0.52 mg – 2.28 mg	0.52 mg – 2.28 mg	2 x 0.25 mg – 9 x 0.25 mg	365.0	3,285 x 0.25 mg
Appropriate comparator therapy					
Captopril OS	0.15 mg/kg = 0.52 mg – 1.14 mg ≙ 0.52 ml – 1.14 ml	1.56 mg - 3.42 mg ≙ 1.56 ml - 3.42 ml	3 x 0.5 ml – 3 x 1.1 ml	365.0	1,095 x 0.5 ml = 547.5 ml – 1,095 x 1.1 ml = 1204.5 ml
Abbreviations: OS = oral solution; ODT = orally disintegrating tablet					

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. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

a) Children and adolescents from 1 to ≤ 17 years of age with heart failure

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					
Enalapril 0.25 mg	100 ODT	€ 141.54	€ 2.00	€ 7.21	€ 132.33
Captopril 5 mg/ml	100 OS	€ 150.40	€ 2.00	€ 6.60	€ 141.80
Captopril 12.5 mg[13]	100 TAB	€ 13.29	€ 2.00	€ 0.16	€ 11.13
Sacubitril/ valsartan 6 mg/6 mg	60 GRC	€ 25.04	€ 2.00	€ 0.00	€ 23.04
Sacubitril/ valsartan 24 mg/26 mg	196 FCT	€ 455.98	€ 2.00	€ 0.00	€ 453.98
Sacubitril/ valsartan 97 mg/103 mg	196 FCT	€ 455.98	€ 2.00	€ 0.00	€ 453.98
Abbreviations: FCT = film-coated tablets; GRC = granules for release from capsules; OS = oral solution; ODT = orally disintegrating tablets; TAB = tablets					

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[13]Fixed reimbursement rate

b) Children from birth to < 1 year of age with heart failure

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					
Enalapril 0.25 mg	100 ODT	€ 141.54	€ 2.00	€ 7.21	€ 132.33
Captopril 5 mg/ml	100 OS	€ 150.40	€ 2.00	€ 6.60	€ 141.80
Abbreviations: OS = oral solution; ODT = orally disintegrating tablet					

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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.

Because there are no 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, no costs for additionally required SHI services need to be taken into account.

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:

a) Children and adolescents from 1 to ≤ 17 years of age with heart failure

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.

References:
Product information for enalapril (Aqumeldi); last revised: November 2023

b) Children from birth to < 1 year of age with heart failure

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.

References:
Product information for enalapril (Aqumeldi); last revised: November 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

At its session on 11 October 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 28 November 2023.

On 29 February 2024, the pharmaceutical company submitted a dossier for the benefit assessment of enalapril to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 29 February 2024 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient enalapril.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 May 2024, and the written statement procedure was initiated with publication on the G-BA website on 3 June 2024. The deadline for submitting statements was 24 June 2024.

The oral hearing was held on 8 July 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 6 August 2024, and the proposed draft resolution was approved.

At its session on 15 August 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	11 October 2022	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	28 November 2023	New determination of the appropriate comparator therapy
Working group Section 35a	2 July 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	8 July 2024	Conduct of the oral hearing
Working group Section 35a	17 July 2024 31 July 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	6 August 2024	Concluding discussion of the draft resolution
Plenum	15 August 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 15 August 2024

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

Prof. Hecken