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) Sacubitril/valsartan (new therapeutic indication: chronic heart failure with left ventricular systolic dysfunction, 1 year to 17 years)

of 7 December 2023

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. 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 sacubitril/valsartan (Entresto) was listed for the first time on 1 January 2016 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 26 May 2023, sacubitril/valsartan 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 from 12.12.2008, sentence 7).

On 14 June 2023, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, No. 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 sacubitril/valsartan with the new

therapeutic indication "treatment of symptomatic chronic heart failure with left ventricular systolic dysfunction in children and adolescents aged one year or older" in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 15 September 2023 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 sacubitril/valsartan 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, as well as of the addendum drawn up by the IQWiG on the benefit assessment. 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 sacubitril/valsartan.

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 Sacubitril/valsartan (Entresto) according to the product information

Heart failure in children and adolescents

Entresto is indicated in children and adolescents aged one year or older for treatment of symptomatic chronic heart failure with left ventricular systolic dysfunction (see section 5.1)

Therapeutic indication of the resolution (resolution of 07.12.2023):

Children and adolescents aged 1 to 17 years with symptomatic chronic heart failure with left ventricular systolic dysfunction

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Children and adolescents aged 1 to 17 years with symptomatic chronic heart failure with left ventricular systolic dysfunction

Appropriate comparator therapy for sacubitril/valsartan:

- Captopril or enalapril

[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 para. 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. In addition to sacubitril/valsartan, only the ACE inhibitors captopril, enalapril and digitalis glycosides are approved for the treatment of symptomatic chronic heart failure in infants, children and adolescents.

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

on 3. The following resolutions are relevant for the present therapeutic indication:

Guideline of the G-BA on the combination of requirements for structured treatment programmes according to Section 137f paragraph 2 SGB V (DMP Requirements Guideline/DMP-A-RL).

Currently, there are no resolutions on the early benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the therapeutic indication of paediatric heart failure.

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"[2] has not been updated for more than 5 years and is currently being revised. The statements in the aforementioned guideline and the scientific-medical societies agree that the guideline-based therapy options for adults with chronic heart failure are generally adopted for the treatment of children and adolescents with chronic heart failure. ACE inhibitors, AT1 receptor blockers, beta-adrenoceptor antagonists, diuretics, mineralocorticoid receptor antagonists and digitalis glycosides may be used here. Digitalis glycosides in particular are recommended with low priority and are only considered as additional reserve medication if patients with HFrEF and sinus rhythm remain significantly symptomatic despite optimum therapy.

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.

[2] AWMF register number 023/006 last revised 31.10.2015, valid until 30.10.2020

The medicinal product "Aqumeldi" with the ACE inhibitor enalapril is a newly approved treatment option for children (from birth) and adolescents with heart failure. The active ingredient enalapril was only recently approved as a paediatric dosage form (marketing authorisation on 15 November 2023).

In summary, neither high-quality evidence from randomised controlled clinical studies 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.

Accordingly, captopril or enalapril is determined as the appropriate comparator therapy on the basis of the generally recognised state of medical knowledge and taking into account the approved active ingredients for the therapeutic indication.

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.

Change of the appropriate comparator therapy

For children and adolescents aged 1 to 17 years with symptomatic chronic heart failure with left ventricular systolic dysfunction, therapy according to doctor's instructions was originally determined as the appropriate comparator therapy. ACE inhibitors, AT1 receptor blockers, beta-adrenoceptor antagonists, diuretics, mineralocorticoid receptor antagonists and digitalis glycosides were categorised as suitable potential comparators that could be considered as therapy according to doctor's instructions as part of a study. As a result of the ruling of the Federal Social Court (FSC) of 22.02.2023 (file ref.: B 3 KR 14/21 R), the medicinal products, which do not have a marketing authorisation for the present indication, cannot be generally considered as appropriate comparator therapy in the narrower sense within the meaning of Section 2, paragraph 1, sentence 3, Section 12 SGB V. This required a new determination of the appropriate comparator therapy, which was changed to best supportive care at the start of the procedure in June 2023.

Captopril and enalapril, which are approved and already regularly used in healthcare, are two established therapy options for treating children and adolescents with heart failure.

The active ingredient enalapril was only recently approved as a paediatric dosage form; however, enalapril was already part of the therapy standard in the off-label use in the therapeutic indication prior to the marketing authorisation and is therefore considered part of the appropriate comparator therapy despite the recent marketing authorisation due to its already established use in the therapeutic indication.

Against this background and in view of the lack of evidence for the off-label use of other active ingredients in paediatric heart failure, the requirements according to Section 6, paragraph 2,

sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) for naming the other active ingredients recommended in the guideline for off-label use are not met, and it is appropriate to designate captopril or enalapril as appropriate comparator therapy.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of sacubitril/valsartan is assessed as follows:

Children and adolescents aged 1 to 17 years with symptomatic chronic heart failure with left ventricular systolic dysfunction

An additional benefit is not proven.

Justification:

The double-blind randomised controlled trial PANORAMA-HF was presented for the assessment of the additional benefit of sacubitril/valsartan for the treatment of heart failure in children aged 1 year or older and adolescents. The study compared the treatment of sacubitril/valsartan versus enalapril in children aged 1 month or older and adolescents. The relevant sub-population for the early benefit assessment comprises children aged 1 year or older and adolescents up to 17 years.

According to the inclusion criteria, chronic heart failure due to left ventricular systolic dysfunction, defined as an LVEF[3] ≤ 45% or LVFS[4] ≤ 22.5%, had to be present. In addition, the children and adolescents had to have a disease severity according to NYHA[5]- or Ross class in the ≥ 2 range, depending on their age. Children aged 6 years or older who had NYHA class I at the time of screening could be enrolled in the study, provided that they had been categorised as class ≥ II at an earlier stage.

The treatment duration, either with sacubitril/valsartan or enalapril, in the study was 52 weeks. In addition to the study medication, the children and adolescents included in both study arms should continue their background therapy for chronic heart failure and any comorbidities. An exception was made for ACE inhibitors, AT1 receptor blockers and renin inhibitors which were not permitted during the entire treatment duration.

The primary endpoint of the study was a composite endpoint, which was recorded as a global rank endpoint and comprises the mortality endpoint as well as various endpoints in the categories of morbidity and health-related quality of life. Further endpoints including the categories of side effects were recorded.

Treatment with enalapril in the comparator arm corresponds to the appropriate comparator therapy. The study is used for the early benefit assessment.

[3] LVEF = left ventricular ejection fraction
[4] LVFS = left ventricular fraction shortening
[5] NYHA = New York Heart Association

Extent and probability of the additional benefit

Mortality

Overall mortality and cardiovascular death presented additionally

There are no statistically significant differences between the treatment arms, neither for the endpoint "overall mortality" nor for the endpoint *"cardiovascular death"* presented additionally.

Morbidity

Severe heart failure events:

- *"UNOS[6] status 1A for heart transplantation"*
- *"VAD[7]/ ECMO[8]/ mechanical ventilation/ intra-aortic balloon pump required for life support"*
- *"Hospitalisation due to heart failure"*
- *"Total hospitalisation"*

There were no statistically significant differences between the treatment arms for the above-mentioned endpoints which represent severe heart failure events.

Symptomatology: PGIS, PGIC

The endpoint "symptomatology" was recorded using PGIS[9] or PGIC[10]. For both endpoints, there are no statistically significant differences between the treatment arms.

Quality of life

The PedsQL[11] questionnaire was used for the health-related quality of life endpoint category in children aged 5 years or older. The parent-reported version of the questionnaire was used for younger children.

The PedsQL measures the general health-related quality of life in children and adolescents. It consists of four multidimensional scales (Physical Functioning, Emotional functioning, Social functioning, and School functioning) with a total of 23 items and three sum scores: Total score, physical health summary score, psychosocial health summary score. The questionnaire consists of a Likert scale from 1 to 4 (1 = best function [never] to 4 = worst function [always]). The scores are then transformed into a scale of 1 to 100; higher scores indicate a higher quality of life. The PedsQL is an established and adequately validated generic instrument for assessing the quality of life in pediatric populations with chronic conditions.

There are no statistically significant differences in the sacubitril/valsartan arm compared with the enalapril arm for the PedsQL endpoint, neither in the patient-reported nor in the parent-reported version.

[6] UNOS = United Network of Organ Sharing
[7] VAD = Ventricular Assist Device
[8] ECMO = extracorporeal membrane oxygenation
[9] PGIS = Patient Global Impression of Severity
[10] PGIC = Patient Global Impression of Change
[11] PedsQL = Paediatric Quality of Life Inventory

Side effects

Overall rates

Serious adverse events (SAEs) and discontinuation due to adverse events (AEs)

There were no statistically significant differences between the treatment arms for the endpoint SAE and discontinuation due to AEs.

Specific AEs

Angio-oedema (AE), hyperkalaemia (SAE) and hypotension (SAE)

In detail, there are no statistically significant differences between the treatment arms for the specific AEs/SAEs of angio-oedema (AE), hyperkalaemia (SAE) and hypotension (SAE).

Nervous system disorders (SAE)

In detail, there is a statistically significant difference in favour of sacubitril/valsartan compared to the enalapril arm in the specific SAE of nervous system disorders.

Overall assessment

For the early benefit assessment of sacubitril/valsartan for the new therapeutic indication for the treatment of paediatric heart failure, the pharmaceutical company is presenting the randomised, double-blind PANORAMA-HF study for a comparison between sacubitril/valsartan and enalapril. The population relevant for the marketing authorisation comprises children aged 1 year or older to adolescents up to 17 years of age with symptomatic chronic heart failure with left ventricular systolic dysfunction. The children and adolescents in the study were treated with either sacubitril/valsartan or enalapril for a total of 52 weeks. Background therapy for chronic heart failure and any comorbidities could be continued during the study, with the exception of ACE inhibitors, AT1 receptor blockers and renin inhibitors, which were not permitted during the study, except for enalapril in the control arm. Treatment with enalapril in the comparator arm corresponds to the determined appropriate comparator therapy.

Endpoints in the categories of mortality, morbidity, health-related quality of life and side effects were assessed in the study. The primary endpoint of the study was a global rank composite endpoint and included endpoints from several categories.

For the mortality category, for the endpoint "overall mortality" and for the endpoint "cardiovascular mortality" presented additionally, there are no statistically significant differences between the treatment arms.

There were no statistically significant differences between the treatment arms in the morbidity category for endpoints relating to symptomatology and severe heart failure events, including hospitalisations due to heart failure, as well as in the health-related quality of life category.

For the side effects, there are no statistically significant differences between the groups for the overall rates of SAEs and for the endpoint "discontinuation due to AEs". In detail, there are no statistically significant differences between the sacubitril/valsartan arm and the enalapril arm for the specific endpoints of angio-oedema (AE), hyperkalaemia (SAE) and hypotension (SAE), while there is a statistically significant difference in favour of sacubitril/valsartan for nervous system disorders (SAE).

Overall, there are no differences between sacubitril/valsartan and the appropriate comparator therapy enalapril that are relevant for the benefit assessment. An additional benefit of sacubitril/valsartan is therefore not proven.

2.1.4 Summary of the assessment

The present assessment is an early benefit assessment of the medicinal product Entresto with the fixed combination of active ingredients sacubitril/valsartan in a new therapeutic indication for the treatment of children and adolescents aged 1 to 17 years with symptomatic chronic heart failure with left ventricular systolic dysfunction.

The G-BA determined captopril or enalapril as the appropriate comparator therapy.

The pharmaceutical company submits the PANORAMA-HF study. Treatment with sacubitril/valsartan was compared with enalapril over a period of 52 weeks. Children aged 1 month to 17 years were enrolled in the study. Relevant for the benefit assessment is the population according to the marketing authorisation from the age of 1 year. The administration of enalapril in the comparator arm of the study corresponds to the appropriate comparator therapy. The study is used for the early benefit assessment.

In the overall assessment of the results in the categories of mortality, morbidity, health-related quality of life and side effects, there are no relevant differences for the benefit assessment between the treatment arms. An additional benefit is 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. Due to various uncertainties[12] in determining the patient numbers, it can be assumed that the SHI target population tends to be underestimated overall.

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 Entresto (active ingredient: sacubitril/valsartan) at the following publicly accessible link (last access: 6 November 2023):

https://www.ema.europa.eu/en/documents/product-information/entresto-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 November 2023).

[12] IQWiG dossier assessment sacubitril/valsartan, heart failure in children and adolescents from 31.10.2023

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 1-year-old children is 11.6 kg, of 5 year olds 20.8 kg, of 6 year olds 23.6 kg and of 17 year olds 67.0 kg[13].

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 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 2 years < 6 years of age, depending on body weight or body surface area 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 children with a body weight of 20.8 kg.

At the time of the resolution, the medicinal product "Aqumeldi" with the active ingredient enalapril for paediatric use in children with heart failure is not yet on the market, so that the costs for an enalapril formulation are presented here on a transitional basis.

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				
Sacubitril/valsartan	Continuously, 2 x daily	365.0	1	365.0
Appropriate comparator therapy				
Captopril	Continuously, 3 x daily	365.0	1	365.0

[13] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Enalapril	Continuously, 1 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 comorbidities, 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.

Designation of the therapy	Dosage/ application	Dose/ subject/ treatment days	Consumption by potency/ treatment day	Treatment days/ subject/ year	Average annual consumption by potency
Medicinal product to be assessed					
Sacubitril/valsartan GRC	**Children under 40 kg BW**				
	3.1 mg/kg BW[14] = 36 mg[15]	72 mg	6 x (6 mg/ 6 mg)	365.0	2,190 x (6 mg/ 6 mg)
Sacubitril/valsartan FCT	**Children above 40 kg BW**				
	(72 mg/ 78 mg) – (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)
Appropriate comparator therapy					
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	0.3 mg/kg = 20.1 mg	56.25 mg	3 x 12.5 mg +	365.0	1,095 x 12.5 mg +

[14] Refers to the total amount of sacubitril and valsartan according to the product information.
[15] The average body weight of 1-year olds (11.6 kg) is used as the basis for calculating the dosage of the lower range.

Designation of the therapy	Dosage/ application	Dose/ subject/ treatment days	Consumption by potency/ treatment day	Treatment days/ subject/ year	Average annual consumption by potency
			3 x ½ 12.5 mg		1,095 x ½ 12.5 mg
Enalapril	0.15 mg/kg – 0.3 mg/kg = 1.74 mg – 20 mg[16]	1.74 mg – 20 mg	1 x 1.74 mg – 1 x 20 mg	365.0	365 x 1.74 mg – 365 x 20 mg
Abbreviations: FCT = film-coated tablets; GRC = granules for release from capsules; OS = oral solution; TAB = tablets					

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.

Composition and costs of prescription medicinal products containing enalapril (capsules):

The calculation of the costs was based on the general instructions and formulation notes for capsule production of the DAC/NRF[17]. For the manufacture of prescription medicinal products, a fixed surcharge of 90% of the pharmacy purchase prices (PPP) of the substances to be used and the required packaging is initially incurred; in addition, both a prescription surcharge and a fixed surcharge in accordance with Section 5, paragraph 1 AMPreisV are incurred.

Mannitol - silicon dioxide filler

Active ingredient	Quantity in g	PPP	Quantity required	Price	Surcharge 90%
Mannitol	100	€ 4.09	99.5	€ 4.07	€ 7.73
Silicon dioxide	100	€ 13.90	0.5	€ 0.07	€ 0.13
		Total	***100***	***€ 4.14***	***€ 7.86***

Enalapril maleate 1.74 mg (60 capsules)

Active ingredient	Quantity in g	PPP	Quantity required for 60 capsules	Price	Surcharge 90%
Enalapril maleate	5	€ 48.80	0.1148	€ 1.12	€ 2.13
Mannitol silicon	100	€ 4.14	14.5852	€ 0.60	€ 1.15

[16] The maximum dose is 20 mg enalapril daily
[17] DAC/NRF = German Drug Codex/ New German Formulary

Gelatine capsules	1	€ 0.01	60	€ 0.60	€ 1.14
Wide-mouth jar	150	€ 0.72	1	€ 0.72	€ 1.37
				Total	***€ 5.78***
Plus surcharges and VAT.					
Prescription surcharge					€ 24.00
Fixed surcharge					€ 8.35
				Subtotal	*€ 38.13*
VAT					€ 7.25
				Cost per pack	**€ 45.38**

Enalapril maleate 20 mg (60 capsules)

Active ingredient	Quantity in g	PPP	Quantity required for 60 capsules	Price	Surcharge 90%
Enalapril maleate	5	€ 48.80	1.3200	€ 12.88	€ 24.48
Mannitol silicon	100	€ 4.14	13.3800	€ 0.55	€ 1.05
Gelatine capsules	1	€ 0.01	60	€ 0.60	€ 1.14
Wide-mouth jar	150	€ 0.72	1	€ 0.72	€ 1.37
				Total	***€ 28.04***
Plus surcharges and VAT.					
Prescription surcharge					€ 24.00
Fixed surcharge					€ 8.35
				Subtotal	*€ 60.39*
VAT					€ 11.47
				Cost per pack	**€ 71.86**

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Sacubitril/valsartan 6 mg/ 6 mg	60 GRC	€ 25.04	€ 2.00	€ 0.54	€ 22.50
Sacubitril/valsartan 24 mg/ 26 mg	196 FCT	€ 455.98	€ 2.00	€ 17.59	€ 436.39
Sacubitril/valsartan 97 mg/ 103 mg	196 FCT	€ 455.98	€ 2.00	€ 17.59	€ 436.39
Appropriate comparator therapy					
Captopril 5 mg/ 5 ml	100 ml OS	€ 150.40	€ 2.00	€ 6.60	€ 141.80

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
Captopril 12.5 mg[18]	100 TAB	€ 13.29	€ 2.00	€ 0.16	€ 11.13
Enalapril 1.74 mg (Prescription medicinal product)	60 CAP	€ 45.38	€ 2.00	–	€ 43.38
Enalapril 20 mg (Prescription medicinal product)	60 CAP	€ 71.86	€ 2.00	–	€ 69.86
Abbreviations: FCT = film-coated tablets; GRC = granules for release from capsules; CAP = capsules; OS = oral solution; ODT = orally disintegrating tablets; TAB = tablets					

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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.

[18] Fixed reimbursement rate

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.

<u>Concomitant active ingredient:</u>

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:

Children and adolescents aged 1 to 17 years with symptomatic chronic heart failure with left ventricular systolic dysfunction

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 sacubitril/valsartan (Entresto); last revised: June 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 6 June 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 14 June 2023 the pharmaceutical company submitted a dossier for the benefit assessment of sacubitril/valsartan to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 15 June 2023 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 sacubitril/valsartan.

The dossier assessment by the IQWiG was submitted to the G-BA on 7 September 2023, and the written statement procedure was initiated with publication on the G-BA website on 15 September 2023. The deadline for submitting statements was 6 October 2023.

The oral hearing was held on 23 October 2023.

By letter dated 24 October 2023, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 9 November 2023.

On 31 October 2023, the IQWiG submitted a new version of IQWiG's dossier assessment to the G-BA. This version 1.1 dated 31 October 2023 replaces version 1.0 of the dossier assessment dated 7 September 2023. The assessment result was not affected by the changes in version 1.1 compared to version 1.0.

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 28 November 2023, and the proposed resolution was approved.

At its session on 7 December 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	6 June 2023	Determination of the appropriate comparator therapy
Working group Section 35a	17 October 2023	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	23 October 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	31 October 2023 14 November 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	28 November 2023	Concluding discussion of the draft resolution
Plenum	7 December 2023	Adoption of the resolution on the amendment of the AM-RL

Berlin, 7 December 2023

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

Prof. Hecken