Sacubitril/valsartan (heart failure, children and adolescents)

Benefit assessment according to §35a SGB V[1]

EXTRACT

Project: A23-56 Version: 1.1 Status: 31 October 2023

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Sacubitril/Valsartan (Herzinsuffizienz, Kinder und Jugendliche) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Sacubitril/valsartan (heart failure, children and adolescents) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

14 June 2023

Internal Project No.

A23-56

Address of publisher

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondent for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

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Keywords

Sacubitril, Valsartan, Heart Failure, Child – Preschool, Child, Adolescent, Benefit Assessment, NCT02678312

Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
BSG	Bundessozialgericht (Federal Social Court)
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug sacubitril/valsartan. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 14 June 2023.

Research question

The aim of this report is to assess the added benefit of sacubitril/valsartan in comparison with best supportive care (BSC) as the appropriate comparator therapy (ACT) in children and adolescents aged 1 year or older with symptomatic chronic heart failure with left ventricular systolic dysfunction.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of sacubitril/valsartan

Therapeutic indication	**ACT**[a]
Children and adolescents aged 1 year or older with symptomatic chronic heart failure with left ventricular systolic dysfunction	BSC[b, c]

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. In accordance with notes by the G-BA, infants, children and adolescents in both study arms are assumed to receive optimal care. Patients with concomitant symptoms of the underlying disease(s) or risk factors, such as tachycardia, tachypnoea, oedema, ascites, pain, hypertension, or cardiac arrhythmias, must receive individual treatment in accordance with the generally recognized state of scientific knowledge. It should be possible to adapt the basic/concomitant medication to the patients' individual needs in both study arms. In this context, treatment adjustment can comprise both dose adjustments and treatment switches/initiations to respond to newly developed symptoms or the deterioration of existing symptoms.
c. Drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).

ACT: appropriate comparator therapy; BSC: best supportive care; BSG: Federal Social Court; G-BA: Federal Joint Committee; SGB: Social Code Book

When determining the appropriate comparator therapy (ACT), the G-BA pointed out that drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceutical Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the Federal Social Court (BSG) comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).

The company deviated from the G-BA's specification of the ACT by using treatment of physician's choice with enalapril as the ACT. The approach of the company is not followed; the present assessment is conducted in comparison with the ACT specified by the G-BA (see Table 2).

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks are used for deriving the added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

The check for completeness of the study pool identified no relevant study for the direct comparison of sacubitril/valsartan versus the ACT BSC. Based on the comparator therapy it used, the company included the PANORAMA-HF study on the comparison of sacubitril/valsartan versus enalapril in its study pool. In Module 4 B of the dossier, the company presented a subpopulation of this study, which it used for its assessment.

The RCT PANORAMA-HF is not used for the benefit assessment of sacubitril/valsartan, as it did not investigate the comparison with the G-BA's ACT. This is explained below.

Irrespective of the research question described above, the G-BA commissioned IQWiG to conduct an analysis (methodological review and presentation of results) of the data of the PANORAMA-HF study presented in Module 4 B. The results of this analysis are summarized below.

Results

Evidence presented by the company – PANORAMA-HF study

The PANORAMA-HF study is a double-blind RCT comparing sacubitril/valsartan with enalapril in children and adolescents aged 1 month or older with symptomatic chronic heart failure with left ventricular systolic dysfunction.

PANORAMA-HF study did not investigate the comparison with the appropriate comparator therapy

With reference to the BSG judgement of 22 February 2023, the G-BA defined BSC as the ACT for the present research question (see Table 2). BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. Disease-specific therapies are not or no longer regularly considered in the context of BSC. The therapy with enalapril used in the PANORAMA-HF study does not represent a treatment in the sense of BSC and does not correspond to the implementation of the ACT defined by the G-BA. Thus, the G-BA's ACT was

not implemented in the PANORAMA-HF study, and the study is not used for the benefit assessment.

Results on added benefit

As no data for comparison with the ACT are available for the present research question, there is no hint of an added benefit of sacubitril/valsartan; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 presents a summary of the probability and extent of added benefit of sacubitril/valsartan.

Table 3: Sacubitril/valsartan – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Children and adolescents aged 1 year or older with symptomatic chronic heart failure with left ventricular systolic dysfunction	BSC[b, c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. In accordance with notes by the G-BA, infants, children and adolescents in both study arms are assumed to receive optimal care. Patients with concomitant symptoms of the underlying disease(s) or risk factors, such as tachycardia, tachypnoea, oedema, ascites, pain, hypertension, or cardiac arrhythmias, must receive individual treatment in accordance with the generally recognized state of scientific knowledge. It should be possible to adapt the basic/concomitant medication to the patients' individual needs in both study arms. In this context, treatment adjustment can comprise both dose adjustments and treatment switches/initiations to respond to newly developed symptoms or the deterioration of existing symptoms.
c. Drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).

ACT: appropriate comparator therapy; BSC: best supportive care; BSG: Federal Social Court; G-BA: Federal Joint Committee; SGB: Social Code Book

The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Supplementary note on the results of the PANORAMA-HF study

The assessment of the PANORAMA-HF study conducted in accordance with the commission produced the following results:

- Advantage of sacubitril/valsartan versus enalapril for the outcome of nervous system disorders (serious adverse events [SAEs])
- For the overall rates of the outcomes of SAEs and discontinuation due to adverse events (AEs), no usable data are available.

For all other used outcomes, there were neither advantages nor disadvantages of sacubitril/valsartan compared with enalapril.

I 2 Research question

The aim of this report is to assess the added benefit of sacubitril/valsartan in comparison with BSC as the ACT in children and adolescents aged 1 year or older with symptomatic chronic heart failure with left ventricular systolic dysfunction.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of sacubitril/valsartan

Therapeutic indication	**ACT**[a]
Children and adolescents aged 1 year or older with symptomatic chronic heart failure with left ventricular systolic dysfunction	BSC[b, c]

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. In accordance with notes by the G-BA, infants, children and adolescents in both study arms are assumed to receive optimal care. Patients with concomitant symptoms of the underlying disease(s) or risk factors, such as tachycardia, tachypnoea, oedema, ascites, pain, hypertension, or cardiac arrhythmias, must receive individual treatment in accordance with the generally recognized state of scientific knowledge. It should be possible to adapt the basic/concomitant medication to the patients' individual needs in both study arms. In this context, treatment adjustment can comprise both dose adjustments and treatment switches/initiations to respond to newly developed symptoms or the deterioration of existing symptoms.
c. Drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).

ACT: appropriate comparator therapy; BSC: best supportive care; BSG: Federal Social Court; G-BA: Federal Joint Committee; SGB: Social Code Book

When determining the ACT, the G-BA pointed out that drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceutical Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).

The company deviated from the G-BA's specification of the ACT by using treatment of physician's choice with enalapril as the ACT. The approach of the company is not followed; the present assessment is conducted in comparison with the ACT specified by the G-BA (see Table 4).

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks are used for deriving the added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on sacubitril/valsartan (status: 17 April 2023)
- bibliographical literature search on sacubitril/valsartan (last search on 03 April 2023)
- search in trial registries/trial results databases for studies on sacubitril/valsartan (last search on 3 April 2023)
- search on the G-BA website for sacubitril/valsartan (last search on 17 April 2023)

To check the completeness of the study pool:

- search in trial registries for studies on sacubitril (last search on 27 June 2023); for search strategies, see Appendix I A of the full dossier assessment

The check for completeness of the study pool identified no relevant study for the direct comparison of sacubitril/valsartan versus the ACT BSC. Based on the comparator therapy it used, the company included the PANORAMA-HF study [3] on the comparison of sacubitril/valsartan versus enalapril in its study pool. In Module 4 B of the dossier, the company presented a subpopulation of this study, which it used for its assessment (see I Appendix B.2 of the full dossier assessment).

The RCT PANORAMA-HF is not used for the benefit assessment of sacubitril/valsartan, as it did not investigate the comparison with the G-BA's ACT. This is explained below.

Irrespective of the research question presented in Chapter I 2, the G-BA commissioned IQWiG to conduct an analysis (methodological review and presentation of results) of the data of the PANORAMA-HF study presented in Module 4 B. This analysis is shown in I Appendix B of the full dossier assessment, and a summary of the results is provided in Chapter I 5.

Evidence presented by the company – PANORAMA-HF study

The PANORAMA-HF study is a double-blind RCT comparing sacubitril/valsartan with enalapril in children and adolescents aged 1 month or older with symptomatic chronic heart failure with left ventricular systolic dysfunction. For the assessment of the added benefit, the company used a subpopulation (aged 1 year to < 18 years) of the PANORAMA-HF study on the comparison of sacubitril/valsartan with enalapril.

No therapies are approved for the treatment of symptomatic chronic heart failure with left ventricular systolic dysfunction in children and adolescents. With reference to the BSG

judgement of 22 February 2023, the G-BA therefore defined BSC as the ACT for the present research question (see Table 4). BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. Disease-specific therapies are not or no longer regularly considered in the context of BSC. Thus, the approval-compliant use of enalapril in the context of BSC should only have taken place in patients with an indication for enalapril for symptom control in hypertension. However, in the entire study population of the PANORAMA-HF study, only < 10% of patients had a history of hypertension. The therapy with enalapril used in the PANORAMA-HF study therefore does not represent a treatment in the sense of BSC and does not correspond to the implementation of the ACT defined by the G-BA. Consequently, the G-BA's ACT was not implemented in the PANORAMA-HF study, and the study is not used for the benefit assessment.

Conclusion

The PANORAMA-HF study is not used for the assessment of sacubitril/valsartan, as it did not investigate the comparison with the ACT.

I 4 Results on added benefit

No data for comparison with the ACT are available to assess the added benefit of sacubitril/valsartan in children and adolescents aged 1 year or older with symptomatic chronic heart failure with left ventricular systolic dysfunction. There is no hint of an added benefit of sacubitril/valsartan in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit for sacubitril/valsartan in comparison with the ACT.

Table 5: Sacubitril/valsartan – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Children and adolescents aged 1 year or older with symptomatic chronic heart failure with left ventricular systolic dysfunction	BSC[b, c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. In accordance with notes by the G-BA, infants, children and adolescents in both study arms are assumed to receive optimal care. Patients with concomitant symptoms of the underlying disease(s) or risk factors, such as tachycardia, tachypnoea, oedema, ascites, pain, hypertension, or cardiac arrhythmias, must receive individual treatment in accordance with the generally recognized state of scientific knowledge. It should be possible to adapt the basic/concomitant medication to the patients' individual needs in both study arms. In this context, treatment adjustment can comprise both dose adjustments and treatment switches/initiations to respond to newly developed symptoms or the deterioration of existing symptoms.
c. Drugs that are not approved for the present therapeutic indication and whose prescribability in off-label use has also not been recognized by the G-BA in the Pharmaceuticals Directive are generally not considered as ACT in the narrower sense of §2 (para. 1, sentence 3) §12 SGB V, according to the BSG comments on the judgment of 22 February 2023 (reference number: B 3 KR 14/21 R).

ACT: appropriate comparator therapy; BSC: best supportive care; BSG: Federal Social Court; G-BA: Federal Joint Committee; SGB: Social Code Book

The assessment described above concurs with that of the company, which used the PANORAMA-HF study for the benefit assessment, but also categorized the added benefit as not proven.

The G-BA decides on the added benefit.

Supplementary note on the results of the PANORAMA-HF study

The assessment of the PANORAMA-HF study (see I Appendix B of the full dossier assessment) conducted in accordance with the commission produced the following results:

- Advantage of sacubitril/valsartan versus enalapril for the outcome of nervous system disorders (SAEs)
- For the overall rates of the outcomes of SAEs and discontinuation due to AEs, no usable data are available.

For all other used outcomes, there were neither advantages nor disadvantages of sacubitril/valsartan compared with enalapril.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a23-56.html.