Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee 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

At its session on 7 December 2023, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of Sacubitril/valsartan in accordance with the resolution of 16 June 2016:

Sacubitril/valsartan

Resolution of: 7 December 2023
Entry into force on: 7 December 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 26 May 2023):

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 7 December 2023):

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

1. Additional benefit of the medicinal product in relation to the appropriate comparator therapy

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

Appropriate comparator therapy:

- Captopril or enalapril

Extent and probability of the additional benefit of sacubitril/valsartan compared to enalapril:

An additional benefit is not proven.

Study results according to endpoints:[1]

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference for the benefit assessment
Morbidity	↔	No relevant difference for the benefit assessment
Health-related quality of life	↔	No relevant difference for the benefit assessment
Side effects	↔	No relevant difference for the benefit assessment
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n.a.: not assessable		

PANORAMA-HF study: RCT over 52 weeks of treatment; sacubitril/valsartan vs enalapril

Mortality

Endpoint	Sacubitril/valsartan		Enalapril		Sacubitril/valsartan vs enalapril
	N	Median time to event in weeks [95% CI] Patients with event n (%)	N	Median time to event in weeks [95% CI] Patients with event n (%)	HR [95% CI] p value[a]
Overall mortality[b]	182	n.r. 7 (3.8)	184	n.r. 12 (6.5)	0.56 [0.22; 1.43]; 0.225[c]
Cardiovascular mortality[b] (presented additionally)	*182*	*n.r.* *6 (3.3)*	*184*	*n.r.* *11 (6.0)*	*0.52 [0.19; 1.42]; 0.202[c]*

[1] Data from the dossier assessment of the IQWiG (A23-56) and from the addendum (A23-103), unless otherwise indicated.

Morbidity

Endpoint	Sacubitril/valsartan		Enalapril		Sacubitril/valsartan vs enalapril
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Symptomatology					
PGIS[d, e]	149	124 (83.2)[g]	156	129 (82.7)[g]	1.01 [0.91; 1.11][h]; 0.931[i]
PGIC[e, f]	148	133 (89.9)[g]	154	138 (89.6)[g]	1.00 [0.93; 1.08][h]; 0.997[i]
Endpoint	**Sacubitril/valsartan**		**Enalapril**		**Sacubitril/valsartan vs enalapril**
	N	Median time to event in weeks [95% CI] Patients with event n (%)	N	Median time to event in weeks [95% CI] Patients with event n (%)	HR [95% CI] p value[a]
Severe heart failure events					
UNOS status 1A for heart transplantation or equivalent status	182	n.r. 5 (2.7)	184	n.r. 7 (3.8)	0.70 [0.22; 2.20]; 0.541[c]
Life-support VAD/ECMO/ mechanical ventilation/ intra-aortic balloon pump required[j]	182	n.r. 6 (3.3)	184	n.r. 12 (6.5)	0.48 [0.18; 1.29]; 0.147[c]
Hospitalisation due to heart failure	182	n.r. 27 (14.8)	184	n.r. 25 (13.6)	1.10 [0.64; 1.89]; 0.741[c]
Total hospitalisation	182	n.r. 64 (35.2)	184	n.r. 59 (32.1)	1.09 [0.76; 1.55]; 0.636[c]

Health-related quality of life

Endpoint	Sacubitril/valsartan		Enalapril		Sacubitril/valsartan vs enalapril
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
PedsQL[e, k]					
patient-reported[l]	114	18 (15.8)	116	16 (13.8)	1.14 [0.61; 2.13]; 0.670
parent-reported	182	35 (19.2)	184	28 (15.2)	1.26 [0.80; 1.99]; 0.311

Side effects

Endpoint	Sacubitril/valsartan		Enalapril		Sacubitril/valsartan vs enalapril
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Overall rates					
AE (presented additionally)[m]	182	163 (89.6)	184	162 (88.0)	–
SAE[n]	182	57 (31.3)	184	53 (28.8)	1.09 [0.80; 1.49]; 0.683
Discontinuation due to AEs[n]	182	10 (5.5)	184	11 (6.0)	0.92 [0.40; 2.11]; 0.892
Specific adverse events (SOC/PT)					
Angio-oedema (PT, AEs)	182	0 (0.0)	184	1 (0.5)	0.34 [0.01; 8.22]; 0.504
Hyperkalaemia (PT, SAEs)	182	0 (0.0)	184	2 (1.1)	0.20 [0.01; 4.18]; 0.301
Hypotension (PT, SAEs)	182	5 (2.7)	184	2 (1.1)	2.53 [0.50; 12.86]; 0.264
Nervous system disorders (SOC, SAEs)[o]	182	4 (2.2)	184	12 (6.5)	0.34 [0.11; 1.03]; 0.044[p] *AD = 4.3%*

[a] Effect, CI and p value: Cox proportional hazards model, adjusted for age group and NYHA/Ross class.
[b] Deaths were recorded as part of the adverse events.
[c] The HR is not available for the period up to week 52. HR is shown for the period up to the end of study. In the present data basis, it is not assumed that the extended period has a relevant influence on HR.
[d] No deterioration at week 52, percentage of patients without an increase of ≥ 1 point on the scale.
[e] Taking into account the cut-off date of the analysis; surveys that took place later than 58 weeks after the baseline survey were excluded from the analysis.
[f] No deterioration at week 52, percentage of patients with the response categories: much better, better or no change
[g] IQWiG calculation
[h] IQWiG calculation, asymptotic
[i] IQWiG calculation, unconditional exact test (CSZ method)
[j] Time until the first event occurred
[k] Percentage of patients with an increase in the score by ≥ 15% at week 52 compared to the start of study, with a scale range of 0 to 100. Higher (increasing) values mean an improvement of health-related quality of life.
[l] A patient-reported survey of PedsQL was only conducted for patients aged 5 to < 18 years.
[m] Contain events of the underlying disease.
[n] with exclusion of the disease-specific PTs heart failure, acute heart failure, congestive heart failure and ventricular dysfunction
[O] IQWIG calculation, unconditional exact test. Discrepancy between p value (exact) and confidence interval (asymptotic) due to different calculation methods.
[p] Frequently occurring events (PT) in the total study population: Seizure (n = 1 vs n = 4) and syncope (n = 1 vs n = 2).

Abbreviations used:
ECMO: extracorporeal membrane oxygenation, HR: hazard ratio, CI: confidence interval, n: number of patients with (at least 1) event, N: number of patients evaluated, n.r. = not reached, PedsQL: Paediatric Quality of Life Inventory, PGIC: Patient Global Impression of Change, PGIS: Patient Global Impression of Severity, PT: preferred term, RCT: randomised controlled trial, RR: relative risk, SOC: system organ class, SAE: serious adverse event, AE: adverse event, UNOS: United Network of Organ Sharing, VAD: Ventricular Assist Device

2. Number of patients or demarcation of patient groups eligible for treatment

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

approx. 170 - 860 patients

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

4. Treatment costs

Annual treatment costs:

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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Sacubitril/valsartan[2]	€ 821.25 - € 4,875.99
Appropriate comparator therapy:	
Captopril	€ 60.94 - € 9,626.80
Captopril OS[3] 1 year	€ 5,434.49
Captopril OS[3] 5 years	€ 9,626.80
Captopril TAB[4] 5 or 6 years	€ 60.94
Captopril TAB[4] 17 years	€ 182.81
Enalapril[5]	€ 263.90 - € 424.98

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 November 2023)

Costs for additionally required SHI services: not applicable

[2] For the calculation of the costs of sacubitril/valsartan, the dosage form sacubitril/valsartan granules in children weighing less than 40 kg and sacubitril/valsartan film-coated tablets in patients weighing over 40 kg are taken into account.
[3] OS = oral solution
[4] TAB = tablets
[5] At the time the resolution was adopted, no medicinal product with the active ingredient enalapril was yet available on the German market for paediatric use in children with heart failure, so that the costs for an enalapril formulation are presented here on a transitional basis.

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

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

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.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. 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.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 7 December 2023.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 7 December 2023

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

Prof. Hecken