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 Sparsentan (primary immunglobulin A nephropathy)

of 6 February 2025

At its session on 6 February 2025, 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. Annex XII shall be amended in alphabetical order to include the active ingredient Sparsentan as follows:

Sparsentan

Resolution of: 6 February 2025
Entry into force on: 6 February 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 19 April 2024):

Filspari is indicated for the treatment of adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥ 0.75 g/g).

Therapeutic indication of the resolution (resolution of 6 February 2025):

See therapeutic indication according to marketing authorisation.

1. Extent of the additional benefit and significance of the evidence

Sparsentan is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5 Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5 Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

Adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥ 0.75 g/g)

Extent of the additional benefit and significance of the evidence of sparsentan:

Hint for a minor additional benefit

Study results according to endpoints:[1]

Adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥ 0.75 g/g)

[1]Data from the dossier assessment of the G-BA (published on 1. November 2024), and from the amendment to the dossier assessment from 10 January 2025, unless otherwise indicated.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	The data are not assessable.
Morbidity	↑	Advantage when reaching stage 4 or 5 CKD.
Health-related quality of life	n.a.	The data are not assessable.
Side effects	↔	No relevant differences 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		

PROTECT study

- Double-blind RCT of phase III
- Comparison of **sparsentan vs irbesartan**
- Study duration: 114 weeks (110 weeks treatment phase + subsequent 4 weeks prior standard therapy)

Mortality[a]

Endpoint	Sparsentan		Irbesartan		Sparsentan vs irbesartan
	N[b]	Patients with event n (%)	N[b]	Patients with event n (%)	Hazard ratio [95% CI] p value
Mortality					
	202	0 (0.0)	202	1 (0.5)	n.d.

Morbidity[a]

Endpoint	Sparsentan		Irbesartan		Sparsentan vs irbesartan
	N[b]	Patients with event n (%)	N[b]	Patients with event n (%)	Relative risk [95% CI] p value
End Stage Renal Disease (ESRD)[c]					
	202	9 (4.5)	202	11 (5.4)	0.82[d] [0.35; 1.93] 0.82
Reaching stage 4 or 5 CKD					
	202	47 (23.3)	202	65 (32.2)	0.64[e] [0.41; 0.99] 0.03[e]
Total hospitalisation (presented additionally)					
	202	39 (19.3)	202	37 (18.3)	1.05[d] [0.70; 1.58] 0.90

Endpoint	Sparsentan		Irbesartan		Sparsentan vs irbesartan
	N[b]	Median time to event in weeks [95% CI] Patients with event n (%)	N[b]	Median time to event in weeks [95% CI] Patients with event n (%)	Hazard ratio[f] [95% CI] p value[f]
Time to reach ESRD (presented additionally)					
	202	n.a. 9 (4.5)	202	n.a. 11 (5.4)	0.75 [0.31; 1.80] 0.51
Time to reach stage 4 or 5 CKD (presented additionally)					
	202	n.a. 47 (23.3)	202	n.a. 65 (32.2)	0.67 [0.46; 0.97] 0.03

Endpoint	Sparsentan			Irbesartan			Sparsentan vs irbesartan
			Change at week x			Change at week x	LS mean difference[g] [95% CI] p value[h]
	N[b]	MV (SD)	LS mean [95% CI]	N[b]	MV (SD)	LS mean [95% CI]	

Percentage change in the UP/C ratio[i] at week 110 (primary study endpoint, presented additionally)							
Baseline[j]							
	202	1.4 (0.9)	-	202	1.4 (0.9)	-	-
Week 110							
	156	-10.2 (149.6)	-42.83 [-49.75; -34.97]	133	13.3 (79.9)	-4.36 [-15.84; 8.70]	0.60 [0.50; 0.72] < 0.0001
Endpoint	**Sparsentan**			**Irbesartan**			**Sparsentan vs irbesartan**
			Annualised slope[g]			Annualised slope[g]	Slope difference[g] [95% CI] p value[h]
	N[b]	MV (SD)	LS mean [95% CI]	N[b]	MV (SD)	LS mean [95% CI]	
Change in eGFR (slope)[k] up to week 110 (presented additionally)							
Baseline[j]							
	202	56.8 (24.3)	-	202	57.1 (23.6)	-	-
Annualised rate of change at week 110							
	159	-2.3 (4.80)	-2.9 [-3.58; -2.24]	138	-4.2 (5.00)	-3.9 [-4.59; -3.13]	1.0 [-0.03; 1.94] 0.0582

Health-related quality of life

The data are not assessable.

Side effects[a]

Endpoint	**Sparsentan**		**Irbesartan**		**Sparsentan vs irbesartan**
	N[b]	Patients with event n (%)	N[b]	Patients with event n (%)	Relative risk [95% CI] p value
Total adverse events (presented additionally)	202	187 (92.6)	202	177 (87.6)	-
Serious adverse events (SAE)	202	75 (37.1)	202	71 (35.1)	1.06 [0.82; 1.37] 0.76

Severe adverse events (CTCAE grade 3 or 4)[l]	202	24 (11.9)	202	29 (14.4)	0.83 [0.50; 1.37] 0.56
Therapy discontinuation due to adverse events	202	21 (10.4)	202	18 (8.9)	1.17 [0.64; 2.12] 0.74
Severe adverse events according to MedDRA (with an incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)					
No statistically significant differences.					
SAEs according to MedDRA (with an incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)					
No statistically significant differences.					
Adverse events of special interest (with statistically significant difference between the treatment arms)					
Hypotension-related AEs (regardless of severity)	202	58 (28.7)	202	25 (12.4)	2.32 [1.52; 3.55] < 0.001

a. Fatalities and safety endpoints were analysed at week 114 (study phase), efficacy endpoints were analysed at week 110 (treatment phase). Fatalities were recorded using safety.
b. Full analysis set
c. The endpoint "End Stage Renal Disease" (ESRD) is a single component of the composite endpoint "Attainment of a confirmed 40% reduction in eGFR, ESRD or death".
d. Unadjusted RR. Two-tailed 95% Wald confidence interval
e. RR and p value were calculated using a logarithmic binomial model with the factors treatment and randomisation strata (eGFR using the CKD-EPI formula: 30 to < 60 ml/min/1.73 m^2 and ≥ 60 ml/min/1.73 m^2 and urine protein excretion (≤ 1.75 g/day and > 1.75 g/day).
f. HR (incl. 95% CI and p value) calculated using Cox regression model with the factors treatment and randomisation strata (eGFR using CKD-EPI formula: 30 to < 60 ml/min/1.73 m^2 and ≥ 60 ml/min/1.73 m^2 and urinary protein excretion (≤ 1.75 g/day and > 1.75 g/day).
g. Pre-specified analysis. 30 imputed data sets were created using a multiple imputation procedure under the assumption of MAR.
h. p values from the MMRM model.
i. Measurement of the protein excretion of a 24-hour urine sample. The results were compared with the creatinine excretion of the same urine sample. An increase means a deterioration in the subject's condition.
j. Baseline is defined as the last non-missing observation at or prior to administration of the study medication.
k. eGFR (ml/min/1.73m²) was derived using the CKD-EPI formula (GFR = 141 x min (SKr/κ, 1)$^{\alpha}$ x max (SKr/κ, 1)$^{-1.209}$ x 0.993^{age}) for adults. An increase means a deterioration in the subject's condition.
l. The study's own criteria were used for severity grading. On the basis of the available information, it does not appear to be certain whether severe AEs and non-severe AEs were differentiated from each other with sufficient clarity, or reliably collected.

Abbreviations used: AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; ESRD = End Stage Renal Disease; HR = hazard ratio; n.d.: no data available; CI = confidence interval; MAR = missing at random; MMRM = mixed model for repeated measures; N = number of patients analysed; n = number of patients with (at least one) event; n.a. = not applicable; RR = relative risk; vs = versus

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

Adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥ 0.75 g/g)

Approx. 900 – 13,000 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 Filspari (active ingredient: sparsentan) at the following publicly accessible link (last access: 7 August 2024):

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

This medicinal product received a conditional marketing authorisation. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

The concomitant use of sparsentan with angiotensin receptor blockers (ARB) is contraindicated.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Sparsentan	€ 56,639.97

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 January 2025

Costs for additionally required SHI services: not applicable

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:

Adults with primary immunoglobulin A nephropathy (IgAN) with a urine protein excretion ≥1.0 g/day (or urine protein-to-creatinine ratio ≥ 0.75 g/g)

- 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 6 February 2025.

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

Berlin, 6 February 2025

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

Prof. Hecken