

**Patisiran** (reassessment of an orphan drug after exceeding the EUR 30 million turnover limit: hereditary transthyretin-mediated amyloidosis with polyneuropathy (stage 1 or 2))

Resolution of: 16 May 2024  
Entry into force on: 16 May 2024  
Federal Gazette, BAnz AT 17 07 2024 B4

valid until: unlimited

**Therapeutic indication (according to the marketing authorisation of 27 August 2018):**

Onpattro is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy.

**Therapeutic indication of the resolution (resolution of 16 May 2024):**

See therapeutic indication according to marketing authorisation.

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

Adults with hereditary transthyretin mediated amyloidosis (hATTR amyloidosis) with stage 1 or stage 2 polyneuropathy

**Appropriate comparator therapy:**

Tafamidis (only for hATTR-PN stage 1) or vutrisiran

**Extent and probability of the additional benefit of patisiran compared to vutrisiran:**

Indication of a lesser benefit

**Study results according to endpoints:<sup>1</sup>**

Adults with hereditary transthyretin mediated amyloidosis (hATTR amyloidosis) with stage 1 or stage 2 polyneuropathy

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<sup>1</sup> Data from the dossier assessment of the Institute for Quality and Efficiency in Health Care (IQWiG) (A23-118) unless otherwise indicated.

## Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant differences for the benefit assessment.
Morbidity	↔	No relevant differences for the benefit assessment.
Health-related quality of life	∅	No data available.
Side effects	↓↓	Disadvantage for the endpoints of SAEs, severe AEs and in detail specific AEs.
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		

## HELIOS-A study: open-label RCT; patisiran vs vutrisiran over a period of 18 months

### Mortality<sup>a</sup>

Endpoint	Patisiran		Vutrisiran		Patisiran vs Vutrisiran
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value <sup>b</sup>
Overall mortality	42	3 (7.1)	122	2 (1.6)	4.36 [0.75; 25.19] <sup>c</sup> ; 0.078

### Morbidity

Endpoint	Patisiran			Vutrisiran			Patisiran vs Vutrisiran
	N <sup>d</sup>	Values at start of study MV (SD)	Change at month 18 LS MV <sup>e</sup> (SE)	N <sup>d</sup>	Values at start of study MV (SD)	Change at month 18 LS MV <sup>e</sup> (SE)	LS MD [95% CI]; p value <sup>f</sup>
Norfolk QoL-DN total value <sup>g</sup>	38	47.3 (29.9)	3.6 (2.9)	113	47.1 (26.3)	0.9 (1.7)	2.7 [-3.7; 9.2]; 0.401

Physical functions/ large nerve fibres	38	23.0 (14.9)	2.1 (1.6)	113	23.1 (13.8)	-0.3 (0.9)	2.4 [-1.1; 5.9]			
Everyday activities	38	5.0 (5.6)	0.5 (0.6)	113	5.7 (5.7)	1.2 (0.4)	-0.7 [-2.0; 0.7]			
Symptoms	38	11.2 (7.3)	0.4 (0.8)	112	11.0 (6.1)	-0.4 (0.5)	0.7 [-1.0; 2.5]			
Small nerve fibres	38	5.1 (4.5)	0.8 (0.5)	113	4.6 (4.2)	0.9 (0.3)	0.0 [-1.1; 1.1]			
Autonomous functions	38	3.0 (2.8)	-0.2 (0.3)	113	2.7 (2.9)	-0.5 (0.2)	0.3 [-0.4; 0.9]			
10-MWT [m/s]	38	1.01 (0.40)	-0.07 (0.04)	113	1.01 (0.39)	-0.03 (0.03)	-0.04 [-0.14; 0.06]; 0.441			
Health status (EQ- 5D-5L VAS <sup>h</sup> )	37	63.0 (16.1)	-5.3 (2.3)	112	64.5 (18.5)	-0.5 (1.3)	-4.8 [-9.9; 0.3]; 0.067			
R-ODS <sup>h</sup> ( <i>presented additionally</i> )	38	34.0 (10.4)	-2.1 (0.9)	114	34.1 (11.0)	-1.8 (0.5)	-0.2 [-2.2; 1.7]; 0.809			
mNIS +7 total value <sup>g</sup> ( <i>presented additionally</i> )	36	57.7 (33.7)	1.4 (2.8)	115	60.6 (36.0)	0.7 (1.6)	0.77 [-5.44; 6.98]; 0.808			
Endpoint	Vutrisiran		Patisiran			Vutrisiran vs Patisiran				
	N	Patients with event n (%)	N	Patients with event n (%)		RR [95% CI] p value <sup>b</sup>				
Hospitalisations due to any cause <sup>a</sup>	42	17 (40.5)	122	31 (25.4)		1.59 [0.99; 2.57]; 0.067				
Endpoi nt	Patisiran					Vutrisiran				
	N	Improve ment <sup>p</sup> n (%)	Stabilisati on <sup>q</sup> n (%)	Deteriora tion <sup>r</sup> n (%)	Missing values n (%)	N	Improve ment <sup>p</sup> n (%)	Stabilisa tion <sup>q</sup> n (%)	Deteriorati on <sup>r</sup> n (%)	Missing values n (%)
FAP	42	1 (2.4)	36 (85.7)	1 (2.4)	4 (9.5)	122	5 (4.1)	101 (82.8)	9 (7.4)	7 (5.7)
PND	42	1 (2.4)	30 (71.4)	7 (16.7)	4 (9.5)	122	13 (10.7)	82 (67.2)	20 (16.4)	7 (5.7)

## Health-related quality of life

Not collected<sup>i</sup>

## Side effects<sup>a,j</sup>

Endpoint	Patisiran		Vutrisiran		Patisiran vs Vutrisiran
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value <sup>a</sup>
AEs <sup>k</sup> (presented additionally)	42	119 (97.5)	122	119 (97.5)	not applicable
SAEs <sup>k</sup>	42	41 (97.6)	122	32 (26.2)	1.63 [1.03; 2.59] 0.045
Severe AEs <sup>k,l</sup>	42	18 (42.9)	122	19 (15.6)	2.45 [1.39; 4.30] 0.002
Discontinuation due to AEs	42	16 (38.1)	122	3 (2.5)	2.91 [0.61; 13.84] 0.174
Reaction in connection with an infusion	Evaluation unsuitable <sup>m</sup>				
Injury, poisoning and procedural complications (SOC, severe AEs <sup>l</sup> ) <sup>n</sup>	42	3 (7.1)	122	1 (0.8)	8.71 [0.93; 81.52] 0.031
Infections and infestations (SOC, SAE)	42	8 (19.0)	122	9 (7.4)	2.58 [1.07; 6.26] 0.034
Heart failure (SMQ narrow scope, SAE)	42	5 (11.9)	122	1 (0.8)	3.63 [1.02; 12.89] 0.036
Gastrointestinal disorders (SOC, SAE) <sup>s</sup>	42	3 (7.1)	122	1 (0.8)	8.71 [0.93; 81.52] 0.031
General disorders and administration site conditions (SOC, SAE) <sup>t</sup>	42	4 (9.5)	122	1 (0.8)	11.62 [1.34; 101.06] 0.008
<p>a. During the 18-month randomised treatment phase patisiran vs vutrisiran (up to week 84)</p> <p>b. p value: IQWiG calculation, unconditional exact test (CSZ method)</p> <p>c. Effect and CI: IQWiG calculation</p> <p>d. Number of patients considered in the evaluation to calculate the effect estimate; values at the start of study are based on 120 to 122 subjects in the intervention arm and 41 to 42 subjects in the control arm</p> <p>e. from the MMRM evaluation</p>					

- f. Effect, CI and p value: MMRM with unstructured variance matrix, value at the start of the study as continuous covariate, treatment, visit, genotype, age at disease onset and the NIS at baseline (< 50 vs ≥ 50) as categorical factors, interaction term treatment × visit. Effect refers to the change from the start of study at 18 months.
- g. Lower values mean low symptomatology (Norfolk-QoL-DN: Scale range -4 to 136; mNIS+7: Scale range 0 to 304; NIS: Scale range 0 to 244). Negative effects (vutrisiran vs patisiran) mean an advantage for the intervention.
- h. Higher scores mean better health status (EQ-5D-5L VAS, scale range 0 to 100) or lower symptomatology (R-ODS, scale range 0 to 48). Positive effects (vutrisiran vs patisiran) mean an advantage for the intervention.
- i. The pharmaceutical company assigns the Norfolk QoL-DN instrument to health-related quality of life.
- j. contain a relevant percentage of events that can be both side effects and symptoms
- k. Events whose PT included the term amyloid or progression must not be considered.
- l. Severe AEs are operationalised as severe or medically significant but not immediately life-threatening; hospitalisation or prolonged hospitalisation indicated; debilitating; limiting self-care in daily living (e.g. bathing, dressing, undressing, feeding, going to the toilet, taking medication, and not bedridden); or life-threatening consequences; urgent intervention indicated; or death due to adverse events. This definition corresponds in wording to the criteria according to NCI CTCAE grade ≥ 3.
- m. The evaluation submitted by the pharmaceutical company is unsuitable for the benefit assessment, but serious infusion reactions are taken into account in the overall SAE rate.
- n. Included PTs are "fall", "ankle fracture" and "fracture of the foot". The PT "Infusion-related reaction" was not assigned by the pharmaceutical company to the primary SOC "Injury, poisoning and procedural complications", but to the SOC "Immune system disorders".
- o. Discrepancy between p value (exact) and CI (asymptotic) due to different calculation methods.
- p. lower FAP stage or lower PND score at month 18 compared to the start of the study
- q. same FAP stage or PND score at month 18 compared to the start of the study
- r. higher FAP stage or higher PND score at month 18 compared to the start of the study
- s. Included PTs are "constipation" and "lip oedema".
- t. Included PTs are "asthenia", "general deterioration of physical health status", "phlebitis at infusion site", "chest pain", "feeling of warmth" and "swelling face".

Abbreviations used:

10-MWT: 10-metre walk test; CTCAE: Common Terminology Criteria for Adverse Events; CI: confidence interval; LS: Least Squares; MedDRA: Medical Dictionary for Regulatory Activities; MD: mean difference; MMRM: mixed model for repeated measures; MV: mean value; n: number of patients with (at least 1) event; N: number of patients evaluated; NCI: National Cancer Institute; NIS: Neuropathy Impairment Score; Norfolk QoL-DN: Norfolk Quality of Life-Diabetic Neuropathy; PT: preferred term; SMQ: standardised MedDRA query; SOC: system organ class; RCT: randomised controlled trial; RR: relative risk; SD: standard deviation; SE: standard error; SAE: serious adverse event; AE: adverse event; VAS: visual analogue scale

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

### Adults with hereditary transthyretin mediated amyloidosis (hATTR amyloidosis) with stage 1 or stage 2 polyneuropathy

approx. 360 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 Onpattro (active ingredient: patisiran) at the following publicly accessible link (last access: 9 February 2024):

[https://www.ema.europa.eu/en/documents/product-information/onpattro-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/onpattro-epar-product-information_en.pdf)

Treatment with patisiran should only be initiated and monitored by doctors experienced in therapy of amyloidosis.

#### 4. Treatment costs

##### Annual treatment costs:

Adults with hereditary transthyretin mediated amyloidosis (hATTR amyloidosis) with stage 1 or stage 2 polyneuropathy

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Patisiran	€ 435,300.50
Additionally required SHI services:	€ 229.67
Appropriate comparator therapy:	
Tafamidis	€ 150,075.47
Vutrisiran	€ 300,961.08

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 May 2024)

**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 hereditary transthyretin mediated amyloidosis (hATTR amyloidosis) with stage 1 or stage 2 polyneuropathy

- 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.