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
Vutrisiran (Hereditary transthyretin-mediated amyloidosis with polyneuropathy (stage 1 or 2))

of 6 April 2023

At its session on 6 April 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. Annex XII shall be amended in alphabetical order to include the active ingredient Vutrisiran as follows:

Vutrisiran

Resolution of: 6 April 2023
Entry into force on: 6 April 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 15 September 2022):

Amvuttra 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 6 April 2023):

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 patisiran

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

Indication of a minor additional benefit

Study results according to endpoints:[1]

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

1 Data from the dossier assessment of the IQWiG (A22-114) and from the addendum (A23-12), 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	↑↑	Advantage 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: Vutrisiran vs patisiran; open-label RCT

Mortality[a]

Endpoint	Vutrisiran		Patisiran		Vutrisiran vs Patisiran
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[b]
Overall mortality	122	2 (1.6)	42	3 (7.1)	0.23 [0.04; 1.33][c]; 0.078

Morbidity

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

Physical functions/ large nerve fibres	113	23.1 (13.8)	-0.3 (0.9)	38	23.0 (14.9)	2.1 (1.6)	-2.4 [-5.9; 1.1]
Everyday activities	113	5.7 (5.7)	1.2 (0.4)	38	5.0 (5.6)	0.5 (0.6)	0.7 [-0.7; 2.0]
Symptoms	112	11.0 (6.1)	-0.4 (0.5)	38	11.2 (7.3)	0.4 (0.8)	-0.7 [-2.5; 1.0]
Small nerve fibres	113	4.6 (4.2)	0.9 (0.3)	38	5.1 (4.5)	0.8 (0.5)	0.0 [-1.1; 1.1]
Autonomous functions	113	2.7 (2.9)	-0.5 (0.2)	38	3.0 (2.8)	-0.2 (0.3)	-0.3 [-0.9; 0.4]
10-MWT [m/s]	113	1.01 (0.39)	-0.03 (0.03)	38	1.01 (0.40)	-0.07 (0.04)	0.04 [-0.06; 0.14]; 0.441
Health status (EQ-5D-5L VAS[h])	112	64.5 (18.5)	-0.5 (1.3)	37	63.0 (16.1)	-5.3 (2.3)	4.8 [-0.3; 9.9]; 0.067
R-ODS[h] *(presented additionally)*	114	34.1 (11.0)	-1.8 (0.5)	38	34.0 (10.4)	-2.1 (0.9)	0.2 [-1.7; 2.2]; 0.809
mNIS +7 total value[g] (presented additionally)	115	60.6 (36.0)	0.7 (1.6)	36	57.7 (33.7)	1.4 (2.8)	-0.8 [-7.0; 5.4]; 0.808

Endpoint	**Vutrisiran**		**Patisiran**		**Vutrisiran vs Patisiran**
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[b]
Hospitalisations due to any cause[a]	122	31 (25.4)	42	17 (40.5)	0.63 [0.39; 1.01] 0.067

Endpoint	**Vutrisiran**					**Patisiran**				
	N	Improvement[p] n (%)	Stabilisation[q] n (%)	Deterioration[r] n (%)	Missing values n (%)	N	Improvement[p] n (%)	Stabilisation[q] n (%)	Deterioration[r] n (%)	Missing values n (%)
FAP	122	5 (4.1)	101 (82.8)	9 (7.4)	7 (5.7)	42	1 (2.4)	36 (85.7)	1 (2.4)	4 (9.5)
PND	122	13 (10.7)	82 (67.2)	20 (16.4)	7 (5.7)	42	1 (2.4)	30 (71.4)	7 (16.7)	4 (9.5)

Health-related quality of life

Not assessed[i]

Side effects[a,j]

Endpoint	Vutrisiran		Patisiran		Vutrisiran vs Patisiran
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
AEs[k] (presented additionally)	122	119 (97.5)	42	41 (97.6)	not applicable
SAEs[k]	122	32 (26.2)	42	18 (42.9)	0.61 [0.39; 0.97] 0.045
Severe AEs [k,l]	122	19 (15.6)	42	16 (38.1)	0.41 [0.23; 0.72] 0.002
Discontinuation due to AEs	122	3 (2.5)	42	3 (7.1)	0.34 [0.07; 1.64] 0.174
Injury, poisoning and procedural complications (SOC, severe AEs[l])[n]	122	1 (0.8)	42	3 (7.1)	0.12 [0.01; 1.07] 0.031[o]
Infections and infestations (SOC, SAE)	122	9 (7.4)	42	8 (19.0)	0.39 [0.16; 0.94] 0.034
Heart failure (SMQ narrow scope, SAE)	122	4 (3.3)	42	5 (11.9)	0.28 [0.08; 0.98] 0.036
Gastrointestinal disorders (SOC, SAE)[s]	122	1 (0.8)	42	3 (7.1)	0.11 [0.01; 1.07][c] 0.031
General disorders and administration site conditions (SOC, SAE)[t]	122	1 (0.8)	42	4 (9.5)	0.09 [0.01; 0.749][c] 0.008

a. during the 18-month randomised treatment phase of vutrisiran vs patisiran; including events that occurred after the 18-month randomised treatment phase of vutrisiran vs patisiran but before the first dose of vutrisiran in the extension phase, i.e. + 84 days in the vutrisiran arm and + 28 days in the patisiran arm
b. p value: IQWiG calculation, unconditional exact test (CSZ method)

c. Effect and CI: IQWiG calculation
d. Number of patients considered in the evaluation to calculate the effect estimate; values at the start of the study are based on 120 to 122 subjects in the intervention arm and 41 to 42 subjects in the control arm
e. from the MMRM evaluation
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 the 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" were not 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

<u>Adults with hereditary transthyretin mediated amyloidosis (hATTR amyloidosis) with stage 1 or stage 2 polyneuropathy</u>

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 Amvuttra (active ingredient: vutrisiran) at the following publicly accessible link (last access: 22 November 2022):

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

Treatment with vutrisiran 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:	
Vutrisiran	€ 481,013.20
Appropriate comparator therapy:	
Patisiran	€ 416,486.57
Additionally required SHI services	€ 225.50
Tafamidis	€ 143,611.44

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 March 2023)

5. 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 Vutrisiran

Medicinal products with the new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients that can be used in a combination therapy with vutrisiran for the treatment of hATTR amyloidosis with polyneuropathy of stage 1 or stage 2 on the basis of the marketing authorisation granted under Medicinal Products Act:

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

- No active ingredient that can be used in a combination therapy that 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 April 2023.

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

Berlin, 6 April 2023

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

Prof. Hecken