Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) 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

Contents

1. Legal basis ... 2

2. Key points of the resolution ... 2

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy ... 3

2.1.1 Approved therapeutic indication of Vutrisiran (Amvuttra) in accordance with the product information ... 3

2.1.2 Appropriate comparator therapy ... 3

2.1.3 Extent and probability of the additional benefit ... 5

2.1.4 Summary of the assessment ... 9

2.2 Number of patients or demarcation of patient groups eligible for treatment ... 10

2.3 Requirements for a quality-assured application ... 10

2.4 Treatment costs ... 10

2.5 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 ... 13

3. Bureaucratic costs calculation ... 14

4. Process sequence ... 14

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published online and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient vutrisiran on 15 October 2022 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 13 October 2022.

The active ingredient vutrisiran (Amvuttra) was approved by the European Commission (EC) on 15.09.2022 as a medicinal product for the treatment of rare diseases (orphan drugs) under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999 for the treatment of hereditary transthyretin-mediated amyloidosis with polyneuropathy. The pharmaceutical company has irrevocably notified the Federal Joint

Committee that, despite the orphan drug status for vutrisiran, a benefit assessment is to be carried out with the submission of evidence in accordance with Section 35a, paragraph 1, sentence 3, numbers 2 and 3 SGB V.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 16 January 2023 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of vutrisiran compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, as well the addendum drawn up by the G-BA on the benefit assessment. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods 1 was not used in the benefit assessment of vutrisiran.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

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

2.1.1 Approved therapeutic indication of Vutrisiran (Amvuttra) in accordance with the product information

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):

"see approved therapeutic indication"

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Appropriate comparator therapy for vutrisiran:

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

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven

1 General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

<u>Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:</u>

on 1. In addition to vutrisiran, the active ingredients tafamidis (ATTR-PN stage 1), inotersen (hATTR-PN stages 1 and 2) and patisiran (hATTR-PN stages 1 and 2) are approved in the present therapeutic indication.

on 2. In principle, liver or heart transplantation can be considered as a non-medicinal treatment option in the present therapeutic indication.

on 3. For the therapeutic indication of hereditary ATTR amyloidosis with polyneuropathy, the following resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are available:

- Patisiran (resolution of 22 March 2019)
- Inotersen (resolution of 22 March 2019)
- Tafamidis (resolution of 20 May 2021)

on 4. The generally recognised state of medical knowledge on which the resolution of the G-BA is based, was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication.

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a paragraph 7 SGB V.

Overall, the body of evidence in the approved therapeutic indication is very limited. A Cochrane review, a systematic review and a guideline were identified for the treatment of adults with hereditary transthyretin-mediated amyloidosis with stage 1 or 2 polyneuropathy. These recommend therapy with the approved disease-modifying medicinal products in the present therapeutic indication, although direct comparator studies are not available.

The two medicinal products patisiran and inotersen are approved for the treatment of hereditary ATTR amyloidosis in adult patients with symptomatic stage 1 or 2

polyneuropathy. In addition, the active ingredient tafamidis is approved for use in ATTR amyloidosis with symptomatic stage 1 polyneuropathy only. For all three active ingredients. the following resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are available: Patisiran was found to have major additional benefit (patisiran vs placebo) in an orphan drug assessment. For inotersen, a non-quantifiable additional benefit (inotersen vs placebo) was determined in the orphan drug assessment, as in terms of side effects there was a higher harm under inotersen in the study. Due to a reassessment after the sales threshold of € 50 million was exceeded, the additional benefit of tafamidis is considered not proven in the absence of direct comparator data for the appropriate comparator therapy (patisiran).

The treatment decision to perform a liver or heart transplant strongly depends on a patient-individual risk-benefit assessment and is also only considered for patients who fulfil defined criteria regarding their severity of the disease, general condition and age. It is assumed that liver or heart transplantation will not be considered at the time of therapy with vutrisiran.

Based on the evidence in the present therapeutic indication and taking into account the comparisons assessed in the early benefit assessment, a therapy with tafamidis (only for stage 1 hATTR-PN) or patisiran is determined as an appropriate comparator therapy in the overall assessment for vutrisiran for the treatment of hereditary transthyretin-mediated amyloidosis in adult patients with symptomatic stage 1 or 2 polyneuropathy. Inotersen, on the contrary, is not seen as part of the appropriate comparator therapy at this time due to its efficacy and safety profile.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment order.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5, Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of vutrisiran is assessed as follows:

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

Indication of a minor additional benefit

Justification:

The pharmaceutical company presents the HELIOS-A study for the assessment of the additional benefit of vutrisiran.

The HELIOS-A study is an open-label, randomised, multicentre, phase III study in adult patients with hATTR amyloidosis with an 18-month treatment phase to directly compare vutrisiran with patisiran.

Patients with hATTR amyloidosis who had a Neuropathy Impairment Score (NIS) of 5 to 130, a Polyneuropathy Disability (PND) score ≤ IIIb and a Karnofsky Performance Status (KPS) ≥ 60% at the start of the study were enrolled in the study. Patients who had undergone liver

transplantation or were due to undergo liver transplantation within the 18-month treatment phase and patients with New York Heart Association (NYHA) classification > II were excluded.

164 patients were randomised in a 3:1 ratio to treatment with vutrisiran or patisiran. Treatment with vutrisiran was given subcutaneously every 3 months or patisiran intravenously every 3 weeks for 18 months, according to the product information. Besides treatment with the study medication, any concomitant medication was allowed and documented, except for medication that is causally used against hATTR amyloidosis. Adequate patient-individual treatment could thus be carried out in both study arms.

The primary endpoint of the study was the change in the modified Neurologic Impairment Score +7 (mNIS+7). Further endpoints of the study on morbidity and side effects were collected.

The 18-month treatment phase was followed by a 42-month extension phase and a 1-year observation phase, which, however, do not allow a comparison with the appropriate comparator therapy and are therefore not relevant for the present benefit assessment.

Extent and probability of the additional benefit

Mortality

For the endpoint “overall mortality”, no statistically significant difference was detected between the treatment groups.

Morbidity

Norfolk QoL-DN
The Norfolk QOL-DN questionnaire consists of 35 questions distributed across the domains of physical functioning/ large nerve fibres (15 questions), activities of daily living (5 questions), symptoms (8 questions), small nerve fibres (4 questions) and autonomic functions (3 questions). The patients' answers to individual questions are converted into points and a total value is formed from this, whereby a lower number of points means a lower level of symptomatology. The total value of the Norfolk QoL-DN can reach values from -4 to 136. The questionnaire used has been validated in the present indication and is a suitable instrument for assessing symptomatology and activities of daily living. The pharmaceutical company assigns the Norfolk QoL-DN questionnaire to health-related quality of life. However, the psychological and social dimensions of health-related quality of life are not presented by the Norfolk QOL-DN. It is therefore assigned to morbidity in the present benefit assessment.
For the endpoint “Norfolk QoL-DN”, there is no statistically significant difference between the treatment groups.

Average walking speed (10-MWT)
The 10-MWT records the walking speed over a 10-metre distance and thus, the physical functioning of the patients. The endpoint is considered to be patient-relevant.
For the endpoint “10-MWT”, there is no statistically significant difference between the treatment groups.

Health status (EQ-5D-5L VAS)

The global assessment of health status was recorded by the patients with the EQ-5D VAS (Euro Quality Visual Analogue Scale). This can take a score from 0 to 100, with higher scores representing better health status. The endpoint is considered to be patient-relevant.
For the endpoint “health status”, there is no statistically significant difference between the treatment groups.

Hospitalisations due to any cause
For the endpoint "hospitalisations due to any cause", there is no statistically significant difference between the treatment groups.

Polyneuropathic symptomatology (mNIS+7)
The change in polyneuropathic symptomatology was recorded using the mNIS+7 (modified Neuropathy Impairment Score + 7). The score is based on a neurological examination and is intended to record various aspects of neuropathic symptomatology. It consists of five domains, each with a different weighting: NIS weakness (maximum 192 points; records impairments in muscle power in the lower and upper extremities and in the muscles controlled by cranial nerves), NIS reflexes (maximum 20 points), Quantitative Sensory Testing (QST, maximum 80 points; measures heat and touch sensitivity), the sum of 5 nerve conduction tests (maximum 10 points, measures nerve/stimulus conduction) and for autonomic dysfunction, positional blood pressure (maximum 2 points). The value of the mNIS+7 can range from 0 to 304 points, with higher values indicating more severe limitations.
A full validation of the mNIS+7 was not carried out. No significant validation studies were presented in the dossier for the scales underlying the mNIS+7 either. Furthermore, the criteria for the weighting of the individual domains are not sufficiently set out.
Against the background of the existing uncertainties, the mNIS+7 is presented additionally for the benefit assessment. For the endpoint “mNIS+7”, no statistically significant difference was detected between the treatment groups.

PND score and FAP stage
The change in mobility and neuropathy stage of the patients were recorded via the PND score and the FAP stage by external assessment. A distinction is made between the following stages:
The PND score is differentiated into stage I (sensory disorder in the limbs without motor disorder), II (limited walking ability, no walking aid necessary), IIIA (walking only with a stick or crutch), IIIB (walking only with two sticks or crutches) or IV (wheelchair-bound or bedridden).
The FAP stage is divided into stage 0 (no complaints), I (no mobility limitations, but mild complaints), II (mobility only with walking aid) or III (mobility only with wheelchair or bedridden).
Walking ability, measured by the PND score or FAP stage, is considered patient-relevant.
The significance of a change to a lower FAP stage or to a low PND value can vary from patient to patient and depending on the baseline value. There is also uncertainty, particularly in the case of low FAP stages and PND values, as to whether the doctor's assessment of mobility during the visit reflects the patient's mobility in everyday life with sufficient certainty. The evaluation of the relative risk (RR) of improvement (change to a low FAP stage or to a lower PND value) presented in the dossier cannot be interpreted meaningfully. The information on FAP stages and PND values presented in the dossier is therefore only presented descriptively without effect estimators. Thus, no statements can be made regarding statistical significance and clinical relevance of these results.

Limitations regarding activities of daily living (R-ODS)
The Rasch-built Overall Disability Scale (R-ODS) questionnaire measures the current physical functioning of patients via 24 questions on everyday activities. The total score can take values between 0 and 48, with a higher score indicating lower limitation. The patient-reported estimation of everyday activity is considered to be patient-relevant. The R-ODS has not been validated for patients with hATTR amyloidosis. As there are uncertainties that the R-ODS is suitable to adequately measure physical functioning in patients with hATTR amyloidosis, the endpoint is presented additionally.
For the endpoint "R-ODS", there is no statistically significant difference between the treatment groups.

Quality of life

In the HELIOS-A study, no endpoint that is suitable for mapping health-related quality of life was collected. The "Norfolk QoL-DN" is assigned to the morbidity category.

Side effects

SAEs
For the SAEs, there is a statistically significant difference between the treatment groups to the advantage of vutrisiran.
However, it remains unclear whether the observed effects can be transferred to patients with a NYHA classification > II.

Severe AEs
For the assessment of AE severity grade, only a definition corresponding to the wording of the overarching definition of the National Cancer Institute (NCI) Common-Terminology-Criteria-for-Adverse-Events (CTCAE) grade was used, but not the full CTCAE assessment system, including the specific definitions for many PTs.
For the severe AEs, there is a statistically significant difference between the treatment groups to the advantage of vutrisiran.

Discontinuation due to AEs
For discontinuation due to AEs, there is no statistically significant difference between the treatment groups.

Specific AEs
In detail, for the specific AEs "Injury, poisoning and procedural complications (severe AEs)", "Infections and infestations (SAEs)", "Heart failure (SAEs), "Gastrointestinal disorders (SAEs)" and "General disorders and administration site conditions (SAEs)", there was a statistically significant difference between the treatment groups to the advantage of vutrisiran.

Overall assessment

For the benefit assessment, the open-label, randomised HELIOS-A study is available, in which vutrisiran was compared with patisiran in adult patients with hATTR amyloidosis in an 18-month treatment phase.
In the mortality category, for the endpoint of overall mortality, there is no statistically significant difference between treatment groups.

In the morbidity category, for the endpoints "Norfolk QoL-DN", "Average walking speed (10-MWT)", "Health status (EQ-5D-5L VAS"), "Hospitalisations due to any cause" and "PND score and FAP stage", there are no statistically significant differences between the treatment groups.

In the category of side effects, for SAEs, severe AEs and specific AEs, there are statistically significant differences between the treatment groups to the advantage of vutrisiran. For discontinuation due to AEs, there are no statistically significant differences between the treatment groups.

In the overall assessment of the results, there is a positive effect in the category of side effects which can be classified as low in magnitude.

Reliability of data (probability of additional benefit)

The assessment of the additional benefit is based on the open-label, randomised HELIOS-A study.
The risk of bias is classified as low at study level. However, due to the open-label study design, there are limitations in the endpoint-specific risk of bias.
Since the results on the side effects, from which the additional benefit is derived, predominantly show high significance, an indication of an additional benefit can be derived overall on the available data basis despite the limitation described.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Amvuttra with the active ingredient vutrisiran. Vutrisiran is approved for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adults with stage 1 or stage 2 polyneuropathy. Patisiran was determined to be the appropriate comparator therapy.

For this patient group, the pharmaceutical company is presenting the HELIOS-A study, which is investigating vutrisiran versus patisiran in patients with hATTR amyloidosis.

In the categories of mortality and morbidity, there are no statistically significant differences between the treatment groups.

No suitable data are available for health-related quality of life.

For the category of side effects, for the endpoints "SAEs", "severe AEs" and in detail "specific AEs", there are statistically significant differences between the treatment groups to the advantage of vutrisiran.

In the overall assessment, an indication of a minor additional benefit of vutrisiran over patisiran is derived.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The number of patients is based on the target population in statutory health insurance (SHI).

The resolution is based on the information from the dossier of the pharmaceutical company. These refer to the updated patient numbers of the preliminary resolution on patisiran[2] from 2019.

Overall, the number of patients in the SHI target population is subject to uncertainties. Especially with regard to the changed treatment setting and the identification of undetected hATTR amyloidoses, a higher number in the target population may result.

2.3 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.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 March 2023).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments, e.g. because of side effects or comorbidities, are not taken into account when calculating the annual treatment costs.

2 Resolution on patisiran from 22 March 2019.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Vutrisiran	Continuously, every 3 months	4.0	1	4.0
Appropriate comparator therapy				
Patisiran	Continuously, 1 x every 21 days	17.4	1	17.4
Tafamidis	Continuously, 1 x daily	365.0	1	365.0

Consumption:

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight: 77.0 kg).[3]

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Vutrisiran	25 mg	25 mg	1 x 25 mg	365.0	365.0 x 25 mg
Appropriate comparator therapy					
Patisiran	300 µg/kg = 23.1 mg	23.1 mg	3 x 10 mg	17.4	52.2 x 10 mg
Tafamidis	20 mg	20 mg	1 x 20 mg	365.0	365.0 x 20 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

3 Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Vutrisiran 25 mg	1 SFI	€ 133,305.30	€ 2.00	€ 13,050.00	€ 120,253.30
Appropriate comparator therapy					
Patisiran 10 mg	1 CIS	€ 8,845.67	€ 2.00	€ 865.00	€ 7,978.67
Tafamidis 20 mg	30 SC	€ 13,080.68	€ 2.00	€ 1,275.00	€ 11,803.68
Abbreviations: CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; SC = soft capsules					

LAUER-TAXE® last revised: 15 March 2023

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

According to the patisiran product information, all patients should receive the following premedication 60 minutes prior to administration to reduce the risk of infusion-related reactions: Corticosteroid (dexamethasone 10 mg or equivalent, intravenous), paracetamol (500 mg, oral), H1 blocker (diphenhydramine 50 mg or equivalent, intravenous), and H2 blocker (ranitidine 50 mg or equivalent, intravenous). In this context, premedication medical products that are not available for intravenous use or that are not tolerated can be administered orally as equivalents.

In addition, according to the product information, patients receiving vutrisiran or patisiran should be administered daily oral vitamin A supplementation at a dosage of approximately 2,500 IU to 3,000 IU, or 2,500 IU per day. Vitamin A is not reimbursable, accordingly it is not listed in the costs.

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I of the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129, paragraph 5a SGB V, when a non-prescription medicinal product is dispensed invoiced according Section 300, a medicinal product sale price applies to the insured person in the amount of the sale price of the pharmaceutical company plus the surcharges according to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the valid version of 31 December 2003.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Patisiran							
Dexamethasone 10 mg [4]	10 SFI each 5 mg	€ 17.40	€ 2.00	€ 0.48	€ 14.92	17.4	€ 51.92
Paracetamol 500 mg [4]	20 TAB each 500 mg	€ 3.47	€ 0.17	€ 0.15	€ 3.15	17.4	€ 2.74
Dimetindene 1 mg/10 kg	5 SFI	€ 23.67	€ 2.00	€ 5.81	€ 15.86	17.4	€ 110.39
Cimetidine 5 mg/kg	10 AMP each 200 mg	€ 19.77	€ 2.00	€ 0.40	€ 17.37	17.4	€ 60.45
Abbreviations: AMP = ampoules; SFI = solution for injection; TAB = tablets							

LAUER-TAXE® last revised: 15 March 2023

2.5 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

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

4 Fixed reimbursement rate

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 21 December 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 13 October 2022, the pharmaceutical company submitted a dossier for the benefit assessment of vutrisiran to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 18 October 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient vutrisiran.

The dossier assessment by the IQWiG was submitted to the G-BA on 12 January 2023, and the written statement procedure was initiated with publication on the G-BA website on 16 January 2023. The deadline for submitting written statements was 6 February 2023.

The oral hearing was held on 20 February 2023.

By letter dated 21 February 2023, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 17 March 2023.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 28 March 2023, and the proposed resolution was approved.

At its session on 6 April 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	21 December 2021	Determination of the appropriate comparator therapy
Working group Section 35a	15 February 2023	Information on written statements received; preparation of the oral hearing

Subcommittee on Medicinal Products	20 February 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	1 March 2023 15 March 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee on Medicinal Products	28 March 2023	Concluding discussion of the draft resolution
Plenum	6 April 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 6 April 2023

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

Prof. Hecken