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

of 16 May 2024

Contents

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 on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient patisiran (Onpattro) was listed for the first time on 1 October 2018 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices. Onpattro® for the treatment of hereditary transthyretin-mediated amyloidosis with stage 1 or stage 2 polyneuropathy 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.

At its session on 22 March 2019, the G-BA decided on the benefit assessment of patisiran in the therapeutic indication "Onpattro is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or

stage 2 polyneuropathy" in accordance with Section 35a of the German Social Code, Book V (SGB V).

If the sales of the orphan drug through the statutory health insurance at pharmacy sales prices and outside the scope of SHI-accredited medical care, including value-added tax, exceed an amount of € 30 million in the last twelve calendar months, the pharmaceutical company must submit evidence in accordance with Section 5, paragraphs 1 to 6 within three months of being requested to do so by the Federal Joint Committee, and in this evidence must demonstrate the additional benefit compared to the appropriate comparator therapy.

By letter dated 2 February 2023, the pharmaceutical company was requested to submit a dossier for the benefit assessment according to Section 35a SGB V by 1 December 2023, due to exceeding the € 30 million turnover limit within the period from December 2021 to November 2022. The pharmaceutical company has 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 6 VerfO on 29 November 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 1 March 2024 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 patisiran 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. 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 patisiran.

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 Patisiran (Onpattro) in accordance with the product information

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

1 General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Therapeutic indication of the resolution (resolution of 16.05.2024):

see the 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 patisiran:

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

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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 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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be

assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

on 1. In addition to patisiran, the active ingredients tafamidis (ATTR-PN stage 1), inotersen (hATTR-PN stages 1 and 2) and vutrisiran (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)
- Vutrisiran (resolution pf 6 April 2023)

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 limited. For the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy, a Cochrane review (Magrinelli et al. 2020), a systematic review (Zhao et al. 2019) and a guideline (Condoluci et al. 2021)

could be identified. These recommend therapy with the approved disease-modifying medicinal products in this therapeutic indication.

The two active ingredients vutrisiran 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. In the benefit assessment, a minor additional benefit was identified for vutrisiran compared with patisiran. For inotersen, a non-quantifiable additional benefit (inotersen vs placebo) was determined in the orphan drug benefit assessment. In the absence of direct comparator data, no additional benefit was identified for the active ingredient tafamidis compared with the appropriate comparator therapy.

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 vutrisiran is determined as an appropriate comparator therapy in the overall assessment for patisiran for the treatment of hereditary transthyretin-mediated amyloidosis in adult patients with symptomatic stage 1 or 2 polyneuropathy. The active ingredient 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 mandate.

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 patisiran is assessed as follows:

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

Indication of a lesser benefit.

Justification:

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

The HELIOS-A study is the label-enabling study on vutrisiran comparing vutrisiran with patisiran. The HELIOS-A study is an open, randomised, multicentre phase III study in adult patients with hATTR amyloidosis with an 18-month treatment phase.

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, 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 direct comparator 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 represented 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 in the HELIOS-A study.

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
There was a statistically significant difference in the overall rate of SAEs to the disadvantage of patisiran.
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.

There was a statistically significant difference in the overall rate of severe AEs to the disadvantage of patisiran.

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

Reaction in connection with an infusion
An infusion-related reaction was collected in the HELIOS-A study under the PT "infusion-related reaction". However, due to the open-label study design (without placebo infusion) and regular intravenous administration, events in this PT could only be collected in the intervention arm.

Overall, there are therefore no usable (comparator) data available for the endpoint "infusion-related reaction".

Other 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 to the disadvantage of patisiran.

Overall assessment

For the benefit assessment, the open-label, randomised HELIOS-A study is available, in which patisiran was compared with vutrisiran 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 side effects category, there were statistically significant differences to the disadvantage of patisiran for the endpoints of SAEs, severe AEs and several specific AEs. For the endpoint of discontinuation due to AEs, there were no statistically significant differences between the treatment groups.

Overall, there were therefore neither advantages nor disadvantages of the active ingredient patisiran compared to vutrisiran in the endpoint categories of mortality and morbidity. No suitable data are available for assessment of the quality of life. In the endpoint category of side effects, however, patisiran showed disadvantages compared to vutrisiran in the overall rates of SAEs, severe AEs and in detail for specific AEs.

The overall assessment of the results thus shows only negative effects for the active ingredient patisiran, which are not offset by any positive effects.

The G-BA therefore follows IQWiG's assessment result from the dossier assessment A23-118 of 27 February 2024 and, in accordance with Section 5, paragraph 7, No. 6 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), states that the benefit of patisiran is lesser than the benefit of vutrisiran. This assessment result does not contradict the findings of the regulatory authority on the quality, efficacy and safety of the medicinal product Onpattro (cf. Section 7, paragraph 2, sentence 6 AM-NutzenV), as its statements are based on the placebo-controlled approval study on Patisiran (APOLLO), which is not considered in the present benefit assessment procedure.
For the above reasons, it can therefore be reasonably concluded that the active ingredient patisiran has a lesser benefit than the active ingredient vutrisiran.

The mere finding that the benefit of patisiran is lesser than the benefit of vutrisiran pursuant to Section 5, paragraph 7, No. 6 AM-NutzenV does not mean that the prescription of the active ingredient patisiran is restricted or excluded due to inappropriateness pursuant to Section 92, paragraph 1, sentence 1, half-sentence 4 SGB V, Chapter 4 Section 11, paragraph 1, sentence 2 VerfO.

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 established benefit is derived predominantly show a high significance, the reliability of data is categorised as "indication" despite the limitation described.

2.1.4 Summary of the assessment

The present assessment is a new benefit assessment of the medicinal product Onpattro with the active ingredient patisiran due to the exceeding of the € 30 million turnover limit. Patisiran is approved for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adults with stage 1 or stage 2 polyneuropathy. The active ingredients tafamidis (only for hATTR-PN stage 1) and vutrisiran were determined as the appropriate comparator therapy.

For the benefit assessment, the pharmaceutical company presented the HELIOS-A study, which investigated patisiran versus vutrisiran in adults with hATTR amyloidosis.

In the endpoint 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 endpoint category of side effects, for the endpoints "SAEs", "severe AEs" and in detail "specific AEs", there were statistically significant differences to the disadvantage of patisiran.

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

This assessment result does not contradict the findings of the regulatory authority on the quality, efficacy and safety of the medicinal product Onpattro, as its statements are not based on the HELIOS-A study used here.

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 data is based on the patient numbers from the dossier of the pharmaceutical company. These refer to the patient numbers on patisiran[2] from 2019.

The number of patients in the SHI target population is subject to uncertainty overall. 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 Resolution on patisiran from 22 March 2019.

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 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

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

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 May 2024).

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.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77.7 kg). [3]

3 Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

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				
Patisiran	Continuously, 1 x every 21 days	17.4	1	17.4
Appropriate comparator therapy				
Tafamidis	Continuously, 1 x daily	365.0	1	365.0
Vutrisiran	Continuously, every 3 months	4.0	1	4.0

Consumption:

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					
Patisiran	300 µg/kg = 23.31 mg	23.31 mg	3 x 10 mg	17.4	52.2 x 10 mg
Appropriate comparator therapy					
Tafamidis	20 mg	20 mg	1 x 20 mg	365.0	365.0 x 20 mg
Vutrisiran	25 mg	25 mg	1 x 25 mg	4.0	4.0 x 25 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. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

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					
Patisiran 10 mg	1 CIS	€ 8,845.67	€ 2.00	€ 504.58	€ 8,339.09
Appropriate comparator therapy					
Tafamidis 20 mg	30 SC	€ 13,080.72	€ 2.00	€ 743.75	€ 12,334.97
Vutrisiran 25 mg	1 SFI	€ 79,799.01	€ 2.00	€ 4,556.74	€ 75,240.27
Abbreviations: CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; SC = soft capsules					

LAUER-TAXE® last revised: 1 May 2024

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 5 mg each	€ 17.43	€ 2.00	€ 0.48	€ 14.95	17.4	€ 52.03
Paracetamol 500 mg[4]	20 TAB	€ 3.47	€ 0.17	€ 0.15	€ 3.15	17.4	€ 2.74
Dimetindene 1 mg/10 kg	5 SFI 4 mg each	€ 23.72	€ 2.00	€ 5.29	€ 16.43	17.4	€ 114.35
Cimetidine 5 mg/kg	10 AMP 200 mg each	€ 19.80	€ 2.00	€ 0.40	€ 17.40	17.4	€ 60.55
Abbreviations: AMP = ampoules; SFI = solution for injection; TAB = tablets							

LAUER-TAXE® last revised: 1 May 2024

4 Fixed reimbursement rate

2.5 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

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.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1

SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

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.

Justification for the findings on designation in the present resolution:

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.

References:
Product information for patisiran (Onpattro); Onpattro 2 mg/ml concentrate for the preparation of an infusion solution; last revised: June 2023

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 10 April 2018, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 3 May 2023.

On 29 November 2023, the pharmaceutical company submitted a dossier for the benefit assessment of patisiran to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 6 VerfO.

By letter dated 30 November 2023 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 patisiran.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 February 2024, and the written statement procedure was initiated with publication on the G-BA website on 1 March 2024. The deadline for submitting statements was 22 March 2024.

The oral hearing was held on 8 April 2024.

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 7 May 2024, and the proposed resolution was approved.

At its session on 16 May 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	10 April 2018	Implementation of the appropriate comparator therapy
Subcommittee Medicinal products	3 May 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	3 April 2024	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	8 April 2024	Conduct of the oral hearing
Working group Section 35a	16 April 2024 29 April 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	7 May 2024	Concluding discussion of the draft resolution
Plenum	16 May 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 16 May 2024

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

Prof. Hecken