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)
Risdiplam (new therapeutic indication: spinal muscular atrophy, < 2 months)

of 7 March 2024

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 Risdiplam (Evrysdi) in accordance with the product information 3

2.1.2 Appropriate comparator therapy 3

2.1.3 Extent and probability of the additional benefit 7

2.1.4 Summary of the assessment 9

2.2 Number of patients or demarcation of patient groups eligible for treatment 11

2.3 Requirements for a quality-assured application 11

2.4 Treatment costs 11

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 16

3. Bureaucratic costs calculation 20

4. Process sequence 20

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 risdiplam (Evrysdi) was listed for the first time on 1 May 2021 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 16 August 2023, risdiplam received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334 from 12.12.2008, sentence 7).

On 12 September 2023, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 3 Ordinance on the Benefit Assessment of

Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient risdiplam with the new therapeutic indication: "Patients < 2 months of age with 5q spinal muscular atrophy (SMA) and a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies". The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 15 December 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 risdiplam compared to 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 risdiplam.

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 Risdiplam (Evrysdi) in accordance with the product information

Evrysdi is indicated for the treatment of 5q spinal muscular atrophy (SMA) in patients with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies.

Therapeutic indication of the resolution (resolution of 7 March 2024):

Patients < 2 months of age with 5q spinal muscular atrophy (SMA) and a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Pre-symptomatic patients < 2 months of age with 5q SMA and up to three SMN2 copies

Appropriate comparator therapy for risdiplam:

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

Therapy according to doctor's instructions taking into account nusinersen and onasemnogene abeparvovec

b) Symptomatic patients < 2 months of age with a clinical diagnosis of SMA Type 1

Appropriate comparator therapy for risdiplam:

Therapy according to doctor's instructions taking into account nusinersen and onasemnogene abeparvovec

c) Pre-symptomatic patients < 2 months of age with 5q SMA and four SMN2 copies

Appropriate comparator therapy for risdiplam:

Therapy according to doctor's instructions taking into account nusinersen and BSC

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 risdiplam, the active ingredients nusinersen for the treatment of 5q spinal muscular atrophy and onasemnogene abeparvovec for the treatment of patients with 5q spinal muscular atrophy (SMA) with a biallelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or patients with 5q SMA with a biallelic mutation in the SMN1 gene and up to 3 SMN2 copies are approved in this therapeutic indication.

on 2. A non-medicinal treatment cannot be considered as appropriate comparator therapy in this therapeutic indication.

on 3. In this indication, resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are available for nusinersen (resolution of 20 May 2021), risdiplam (resolution of 21 October 2021) and onasemnogene abeparvovec (resolution of 4 November 2021).

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

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 evidence in the therapeutic indication of SMA is limited. In its resolution of 20 May 2021, the G-BA conducted a new benefit assessment for the active ingredient nusinersen after the € 50 million turnover limit was exceeded. For patients with 5q SMA Type 1, the G-BA found an indication of a major additional benefit for nusinersen compared with the appropriate comparator therapy best supportive care (BSC), and a

hint of considerable additional benefit for patients with 5q SMA type 2, and for pre-symptomatic patients with 5q SMA and 2 SMN2 gene copies a hint for a considerable additional benefit. and for pre-symptomatic patients with 5q SMA and 3 SMN2 gene copies a hint for a non-quantifiable additional benefit. An additional benefit for nusinersen compared to BSC is not proven for patients with 5q SMA Type 3 / 4, as well as for pre-symptomatic patients with 5q SMA and more than 3 SMN2 gene copies. However, the G-BA indicated that nusinersen may be a relevant treatment option for patients with 5q SMA Type 3 / 4 and for pre-symptomatic patients with 5q SMA and more than 3 SMN2 gene copies, taking into account the evidence presented on the medical benefit, the severity of the disease and the opinions of the scientific-medical societies on the current reality of care.

By its resolution of 4 November 2021, the G-BA conducted a benefit assessment for the active ingredient onasemnogene abeparvovec after exceeding the 50 million euro turnover limit. For patients with 5q SMA Type 1, patients with 5q SMA Type 2 and up to 3 SMN2 copies, and pre-symptomatic patients with 5q SMA and up to 3 SMN2 copies, the additional benefit over nusinersen is not proven. For patients with 5q SMA Type 3 and up to 3 SMN2 copies, the additional benefit compared to therapy according to doctor's instructions with nusinersen or BSC is not proven. However, the G-BA has indicated that onasemnogene abeparvovec may be a relevant therapy option for all patient populations assessed, taking into account the available evidence on medical benefit, the severity of the disease and the statements of the scientific-medical societies on the current reality of care.

In addition to a guideline with recommendations for the non-medicinal treatment of SMA, an S1 guideline on the diagnosis and treatment of spinal muscular atrophy (SMA) was also included in the evidence synopsis. For the active ingredients nusinersen and onasemnogene abeparvovec, the guideline describes that clinical studies in infants and children showed improvements in motor function, but according to the findings to date, success depends primarily on the time of treatment and therefore the stage of the disease. In its written submission, the German Scientific-medical Society of Neuropaediatrics (GNP) states that a comparator therapy with onasemnogene abeparvovec or nusinersen is appropriate for patients with SMA Type 1 or up to 3 SMN2 copies and a comparator therapy with nusinersen or best supportive care is appropriate for patients with SMA and with 4 or more SMN2 copies.

Risdiplam is approved for the treatment of 5q SMA in patients with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies. The new therapeutic indication assessed in this procedure only considers patients < 2 months of age. According to the clinical assessment experts, some of the children with two SMN2 copies already have symptoms in the first days of life. Three patient groups are therefore distinguished for the present procedure, depending on the presence of a symptomatic phenotype and the eligible therapies, taking into account the number of SMN2 copies. Patients with a clinical diagnosis of SMA Type 2 and SMA Type 3 are not included in the present therapeutic indication of patients < 2 months of age, taking into account the defined criteria for type categorisation.

Based on the limited evidence available and taking into account the assessment of the scientific-medical societies, a therapy according to doctor's instructions is determined for

a) pre-symptomatic patients < 2 months of age with 5q SMA and up to three SMN2 copies

b) symptomatic patients < 2 months of age with a clinical diagnosis of SMA Type 1,

taking into account nusinersen and onasemnogene abeparvovec as the appropriate comparator therapy for risdiplam and for

c) pre-symptomatic patients < 2 months of age with 5q SMA and four SMN2 copies,

taking into account nusinersen and BSC as the appropriate comparator therapy for risdiplam.

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 risdiplam is assessed as follows:

a) Pre-symptomatic patients < 2 months of age with 5q SMA and up to three SMN2 copies

For pre-symptomatic patients < 2 months of age with 5q SMA and with up to three SMN2 copies, an additional benefit is not proven.

b) Symptomatic patients < 2 months of age with a clinical diagnosis of SMA Type 1

For symptomatic patients < 2 months of age with a clinical diagnosis of SMA Type 1, an additional benefit is not proven.

c) Pre-symptomatic patients < 2 months of age with 5q SMA and four SMN2 copies

For pre-symptomatic patients < 2 months of age with 5q SMA and four SMN2 copies, an additional benefit is not proven.

Justification:

The RAINBOWFISH study is available for the benefit assessment. This is an ongoing single-arm study, in which 26 pre-symptomatic patients with genetic evidence of 5q SMA who were less than 6 weeks old at the time of the first dose of risdiplam were enrolled. There was no restriction on the number of SMN2 copies. 8 patients had 2 SMN2 copies, 13 patients had 3 copies and 5 patients had ≥ 4 copies. According to the study protocol, all enrolled children should receive SMA treatment according to the local standard. Physiotherapy, occupational therapy or other movement therapies were encouraged. The study protocol also explicitly mentioned medicinal products that are generally recommended as suitable supportive therapies in the therapeutic indication, e.g. inhaled drugs such as anticholinergics, antibiotic treatments and laxatives. Ventilation (non-invasive or invasive) was not explicitly permitted as a concomitant treatment in the study protocol, but the time to permanent ventilation was recorded as an endpoint in the study.

The primary endpoint of the study is the percentage of patients with 2 SMN2 copies and a baseline compound muscle action potential (CMAP) amplitude ≥ 1.5 mV who can sit unsupported for 5 seconds after 12 months of treatment. Secondary endpoints are the endpoints on mortality, morbidity and adverse events (AEs). The study includes a screening phase of up to 6 weeks and a treatment phase of 2 years (followed by a ≤ 3-year open-label extension phase).

The study has been conducted since August 2019 in 7 study sites in Australia, Belgium, Brazil, Poland, Russia, Taiwan and the USA.

a) <u>Pre-symptomatic patients < 2 months of age with 5q SMA and up to three SMN2 copies</u>

For pre-symptomatic patients < 2 months of age with up to 3 SMN2 copies, results from the single-arm RAINBOWFISH study are available for the endpoint categories of mortality, morbidity and side effects.

The single-arm RAINBOWFISH study presented by the pharmaceutical company does not allow a comparison with the appropriate comparator therapy.

The pharmaceutical company assumes that the oral or continuous administration of risdiplam offers advantages over the dosage forms of the active ingredients of the appropriate comparator therapy, which includes therapy according to doctor's instructions, taking into account the intrathecal administration of nusinersen and the single administration of onasemnogene abeparvovec. However, for the claimed advantages, no data were presented by the pharmaceutical company.

There is a lack of suitable comparator data for the assessment of the additional benefit of risdiplam compared with the appropriate comparator therapy. An additional benefit is therefore not proven.

Taking into account the available evidence on the medical benefit of risdiplam, the severity of the disease and the statements of the scientific-medical societies on the current reality of care, risdiplam may represent a relevant therapy option for pre-symptomatic patients < 2 month of age with 5q SMA and up to three SMN2 copies.

b) Symptomatic patients < 2 months of age with a clinical diagnosis of SMA Type 1

No data are available for symptomatic patients < 2 months of age with a clinical diagnosis of SMA Type 1. An additional benefit is therefore not proven.

Taking into account the available evidence on the medical benefit of risdiplam, the severity of the disease and the statements of the scientific-medical societies on the current reality of care, risdiplam may represent a relevant therapy option for symptomatic patients < 2 month of age with a clinical diagnosis of SMA Type 1.

c) Pre-symptomatic patients < 2 months of age with 5q SMA and four SMN2 copies

For pre-symptomatic patients < 2 months of age and four SMN2 copies, results from the single-arm RAINBOWFISH study are available for the endpoint categories of mortality, morbidity and side effects. The study enrolled 5 patients with ≥ 4 SMN2 copies, so it is unclear how high the percentage of patients with exactly 4 SMN2 copies.

There is a lack of suitable comparator data for the assessment of the additional benefit of risdiplam compared with the appropriate comparator therapy. An additional benefit is therefore not proven.

Taking into account the available evidence on the medical benefit of risdiplam, the severity of the disease and the statements of the scientific-medical societies on the current reality of care, risdiplam may represent a relevant therapy option for pre-symptomatic patients < 2 month of age with 5q SMA and four SMN2 copies.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient risdiplam. The therapeutic indication assessed here is as follows: Patients < 2 months of age with 5q spinal muscular atrophy (SMA) and a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies.

In the therapeutic indication to be considered, 3 patient groups were distinguished:

a) Pre-symptomatic patients < 2 months of age with 5q SMA and up to three SMN2 copies

The G-BA determined the appropriate comparator therapy to be a therapy according to doctor's instructions under consideration of nusinersen and onasemnogene abeparvovec.

For pre-symptomatic patients < 2 months of age with up to 3 SMN2 copies, results from the single-arm RAINBOWFISH study are available for the endpoint categories of mortality, morbidity and side effects.

The single-arm RAINBOWFISH study presented by the pharmaceutical company does not allow a comparison with the appropriate comparator therapy. Suitable comparator data are therefore lacking for the advantages claimed by the pharmaceutical company that would

result from the oral or continuous administration of risdiplam compared with the appropriate comparator therapy. An additional benefit is not proven.

Taking into account the available evidence on the medical benefit of risdiplam, the severity of the disease and the statements of the scientific-medical societies on the current reality of care, risdiplam may represent a relevant therapy option for pre-symptomatic patients < 2 month of age with 5q SMA and up to three SMN2 copies.

b) Symptomatic patients < 2 months of age with a clinical diagnosis of SMA Type 1

The G-BA determined the appropriate comparator therapy to be a therapy according to doctor's instructions under consideration of nusinersen and onasemnogene abeparvovec.

No data are available for symptomatic patients < 2 months of age with a clinical diagnosis of SMA Type 1. An additional benefit is therefore not proven.

Taking into account the available evidence on the medical benefit of risdiplam, the severity of the disease and the statements of the scientific-medical societies on the current reality of care, risdiplam may represent a relevant therapy option for symptomatic patients < 2 month of age with a clinical diagnosis of SMA Type 1.

c) Pre-symptomatic patients < 2 months of age with 5q SMA and four SMN2 copies

The G-BA determined the appropriate comparator therapy to be a therapy according to doctor's instructions taking into account nusinersen and BSC.

For pre-symptomatic patients < 2 months of age and four SMN2 copies, results from the single-arm RAINBOWFISH study are available for the endpoint categories of mortality, morbidity and side effects. The study enrolled 5 patients with ≥ 4 SMN2 copies, so it is unclear how high the percentage of patients with exactly 4 SMN2 copies.

There is a lack of suitable comparator data for the assessment of the additional benefit of risdiplam compared with the appropriate comparator therapy. An additional benefit is therefore not proven.

Taking into account the available evidence on the medical benefit of risdiplam, the severity of the disease and the statements of the scientific-medical societies on the current reality of care, risdiplam may represent a relevant therapy option for pre-symptomatic patients < 2 month of age with 5q SMA and four SMN2 copies.

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

The information on the number of patients is based on the target population in statutory health insurance (SHI). The G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier.

Notwithstanding the G-BA's finding, the pharmaceutical company divides the target population into patients with up to 3 SMN2 copies and patients with 4 SMN2 copies. The resolution therefore states the number of patients for the entire target population. The specification is plausible in the order of magnitude.

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 Evrysdi (active ingredient: risdiplam) at the following publicly accessible link (last access: 11 December 2023): https://www.ema.europa.eu/en/documents/product-information/evrysdi-epar-product-information_en.pdf.

Treatment with risdiplam should be initiated and monitored by specialists in paediatrics and adolescent medicine with a focus on neuropaediatrics or neurology who are experienced in the treatment of patients with spinal muscular atrophy (SMA).

Molecular genetic diagnostics regarding deletion or mutation of the SMN1 gene including determination of the SMN2 gene copy number for the presence of SMA should be performed.

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 February 2024).

The Robert Koch Institute's reference percentile was used to calculate the dosage for children under one year of age as a function of the body weight[2]. Based on the average body weights of boys and girls, the average body weight for children aged 1 month is 4.35 kg.

The product information specifies a risdiplam dosage of 0.15 mg/ kg for children < 2 months of age. The treatment costs were calculated for 2 months using the average body weight of one-month-old children as an example, even though the individual treatment duration and/or weight may vary during the course of therapy.

According to product information, treatment with nusinersen begins with 4 loading doses on days 0, 14, 28 and 63, followed by a maintenance dose every 4 months. The treatment costs

[2] Robert Koch Institute. Contributions to Federal Health Reporting: Reference percentiles for anthropometric measures and blood pressure from the Study on the Health of Children and Adolescents in Germany (KiGGS) [online]. [Accessed: 19.01.2024]. URL: https://www.rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GBEDownloadsB/KiGGS_Referenzperzentile.pdf?__blob=publicationFile

were calculated for 2 months on the basis of the first 3 loading doses to be administered during this period.

Risdiplam and nusinersen are administered continuously, the costs for children over 2 months of age and the costs for adults are shown in the resolution for the active ingredient risdiplam of 21 October 2021.

Onasemnogene abeparvovec is a gene therapy intended for single use. The product information contains recommended dosages for patients with a body weight of 2.6 kg to 21.0 kg. The treatment costs were calculated using the average body weight of one-month-old children as an example, even though the weight at the time of therapy may vary.

Treatment period:

a) Pre-symptomatic patients < 2 months of age with 5q SMA and up to three SMN2 copies

b) Symptomatic patients < 2 months of age with a clinical diagnosis of SMA Type 1

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Risdiplam	Continuously, 1 x daily	60.8	1	60.8
Appropriate comparator therapy				
Therapy according to doctor's instructions taking into account nusinersen and onasemnogene abeparvovec				
Nusinersen	Day 0, 14, 28	3	1	3
Onasemnogene abeparvovec	Single dose	1	1	1

c) Pre-symptomatic patients < 2 months of age with 5q SMA and four SMN2 copies

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Risdiplam	Continuously, 1 x daily	60.8	1	60.8
Appropriate comparator therapy				
Therapy according to doctor's instructions, taking into account nusinersen and best supportive care				
Nusinersen	Day 0, 14, 28	3	1	3
Best supportive care[3]	Different from patient to patient			

Consumption:

a) Pre-symptomatic patients < 2 months of age with 5q SMA and up to three SMN2 copies

b) Symptomatic patients < 2 months of age with a clinical diagnosis of SMA Type 1

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					
Risdiplam (0.75 mg/ml)	0.15 mg/kg 1 month: 0.65 mg	0.65 mg (0.87 ml)	1 x 0.9 ml	60.8	60.8 x 0.9 ml
Appropriate comparator therapy					
Therapy according to doctor's instructions taking into account nusinersen and onasemnogene abeparvovec					
Nusinersen	12 mg	12 mg	1 x 12 mg	3.0	3.0 x 12 mg

[3] When comparing risdiplam versus best supportive care, the costs of best supportive care must also be additionally considered for the medicinal product to be assessed.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Onasemnogene abeparvovec	1.1×10^{14} vg/kg 1 month: 5.0×10^{14} vg	5.0×10^{14} vg = 24.8 ml	1 x 24.8 ml	1.0	1.0 x 24.8 ml

c) Pre-symptomatic patients < 2 months of age with 5q SMA and four SMN2 copies

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					
Risdiplam (0.75 mg/ml)	0.15 mg/kg 1 month: 0.65 mg	0.65 mg (0.87 ml)	1 x 0.9 ml	60.8	60.8 x 0.9 ml
Appropriate comparator therapy					
Therapy according to doctor's instructions, taking into account nusinersen and best supportive care					
Nusinersen	12 mg	12 mg	1 x 12 mg	3.0	3.0 x 12 mg
Best supportive care	Different from patient to patient				

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.

Onasemnogene abeparvovec is listed in the LAUER-TAXE®, but is only dispensed as a clinic pack. Accordingly, the active ingredient is not subject to the Pharmaceutical Price Ordinance

(Arzneimittelpreisverordnung), and no rebates according to Section 130 or Section 130a SGB V apply. The calculation is based on the purchase price of the clinic pack plus 19% value added tax, in deviation from the LAUER-TAXE® data usually taken into account.

a) Pre-symptomatic patients < 2 months of age with 5q SMA and up to three SMN2 copies

b) Symptomatic patients < 2 months of age with a clinical diagnosis of SMA Type 1

c) Pre-symptomatic patients < 2 months of age with 5q SMA and four SMN2 copies

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					
Risdiplam 60 mg	1 POS	€ 9,091.73	€ 2.00	€ 515.94	€ 8,573.79
Appropriate comparator therapy					
Nusinersen 12 mg	1 SFI	€ 79,680.92	€ 2.00	€ 0.00	€ 79,678.92
Onasemnogene abeparvovec	Packaging size	Costs (clinic purchase)		19% VAT	Costs of the medicinal product
Onasemnogene abeparvovec 2x10E^{13} vector genome/ml 4,5 kg	1 INF	€ 1,385,000.00		€ 263,150.00	€ 1,648,150.00
Best supportive care	Different from patient to patient				
Abbreviations: SFI = solution for injection; INF = infusion solution; POS = powder for preparation of an oral solution					

LAUER-TAXE® last revised: 1 February 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.

Additionally required SHI services for the application of the active ingredient nusinersen result from the intrathecal application via lumbar puncture according to the product information. At the time of the resolution, however, there is no fee structure item in the Uniform Value Scale

for the use of an antisense oligonucleotide, which is why the resulting costs are non-quantifiable.

Type of service Lumbar puncture	Costs per treatment	Number/ patient per year	Costs/ patient per year
2 months	Non-quantifiable	3.0	Non-quantifiable

According to the product information, an AAV9 antibody test with an appropriately validated test must be performed prior to the use of onasemnogene abeparvovec. There is not yet a billing number for the test in the EBM catalogue.

Furthermore, immunomodulatory pre- and concomitant medication with a corticosteroid is required. Due to the weight-dependent dosage and the different durations of therapy, the necessary costs incurred for immunomodulatory therapy are different from patient to patient and are not quantified here.

According to the product information, troponin I level must be measured before Zolgensma is administered and troponin I level must be monitored for at least 3 months after administration. There is only one EBM number in the EBM catalogue for the immunological detection of troponin I for billing in the presence of clinical symptomatology.

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.

<u>Concomitant active ingredient:</u>

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:

a) Pre-symptomatic patients < 2 months of age with 5q SMA and up to three SMN2 copies

- No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

  References:
  Product information for risdiplam (Evrysdi®); Evrysdi® 0.75 mg/ml powder for preparation of an oral solution; last revised: December 2023

b) Symptomatic patients < 2 months of age with a clinical diagnosis of SMA Type 1

- No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

  References:
  Product information for risdiplam (Evrysdi®); Evrysdi® 0.75 mg/ml powder for preparation of an oral solution; last revised: December 2023

c) Pre-symptomatic patients < 2 months of age with 5q SMA and four SMN2 copies

– No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for risdiplam (Evrysdi®); Evrysdi® 0.75 mg/ml powder for preparation of an oral solution; last revised: December 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 12 July 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 12 September 2023 the pharmaceutical company submitted a dossier for the benefit assessment of risdiplam to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 14 September 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits 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 risdiplam.

The dossier assessment by the IQWiG was submitted to the G-BA on 12 December 2023, and the written statement procedure was initiated with publication on the G-BA website on 15 December 2023. The deadline for submitting statements was 5 January 2024.

The oral hearing was held on 22 January 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 27 February 2024, and the proposed resolution was approved.

At its session on 7 March 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	24 January 2024	Determination of the appropriate comparator therapy
Working group Section 35a	16 January 2024	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	22 January 2024	Conduct of the oral hearing
Working group Section 35a	30 January 2024 13 February 2024	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	27 February 2024	Concluding discussion of the draft resolution
Plenum	7 March 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 7 March 2024

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

Prof. Hecken