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 (spinal muscular atrophy)

of 21 October 2021

**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 studies 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 benefits,
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. Costs of therapy for the statutory health insurance,
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 forms part of the Pharmaceuticals Directive.

## 2. Key points of the resolution

The relevant date for the first placing on the (German) market of the active ingredient risdiplam in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1st May 2021. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 23 April 2021.

The active ingredient risdiplam (Evrysdi®) was approved by the European Commission (EC) on 26.03.2021 as a medicinal product for the treatment of rare diseases (orphan drugs) under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December

1999 for the treatment of spinal muscular atrophy. The pharmaceutical company has irrevocably notified the Federal Joint Committee that, despite the orphan drug status for risdiplam, a benefit assessment is to be carried out with the submission of evidence in accordance with Section 35a, paragraph 1, sentence 3, numbers 2 and 3 SGB V.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 2nd August 2021, 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 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, and the addenda to the benefit assessment prepared by IQWiG. 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 2 months of age and older, 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 from 21.10.2021):**

see the approved therapeutic indication

### 2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a. Pre-symptomatic patients two months of age or older with 5q SMA and with one to three copies of the SMN2 gene

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Symptomatic patients two months of age or older with clinically diagnosed 5q SMA type 1 or type 2

Appropriate comparator therapy for risdiplam: Nusinersen

b. Pre-symptomatic patients two months of age and older with 5q SMA with four copies of the SMN2 gene

Symptomatic patients with clinically diagnosed 5q SMA type 3

Appropriate comparator therapy for risdiplam: Treatment according to the doctor's instructions of nusinersen or BSC

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

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to 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 Federal Joint Committee has already determined the patient-relevant benefit 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.

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

on 1. The active ingredient nusinersen is approved for the treatment of 5q spinal muscular atrophy. The active ingredient onasemnogene abeparvovec is approved for the treatment of patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene.

on 2. Supportive measures and symptom treatment include, for example, physiotherapy, occupational therapy as well as voice, speech and language therapy in accordance with the remedies catalogue, surgical measures (e.g. tracheostomy), ventilation, respiratory hygiene, nutrition management, aids.

on 3. For the present therapeutic indication, the G-BA has passed resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient nusinersen, on 20 May 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 § 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 indication according to Section 35a paragraph 7 SGB V (see "Information on Appropriate Comparator Therapy").

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 considerable 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 indicates 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.

Cochrane reviews on the medicinal treatment of patients with spinal muscular atrophy type 1 and for type 2, and 3 and a systematic review on the treatment of SMA with nusinersen were included in the evidence synopsis. Accordingly, treatment with nusinersen to improve motor function is recommended for patients with early and late onset SMA based on a high level of evidence. It should be noted that there is currently insufficient evidence to support efficacy in SMA types 3 and 4 or to initiate treatment in adults.

The evidence synopsis also includes a guideline with recommendations for the non-medicinal treatment of SMA.

There is no aggregate or higher-quality evidence for the active ingredient onasemnogene abeparvovec. A resolution on a benefit assessment for the active ingredient onasemnogene abeparvovec, which will be approved in May 2020, is still pending due to the fact that the €50 million turnover limit has been exceeded. Therefore, and due to the fact that they are not yet available on the market for a long time, the active ingredient cannot be considered as an appropriate comparator therapy for the present procedure.

Based on the available evidence, the G-BA determined nusinersen as an appropriate comparator therapy for pre-symptomatic patients two months of age and older with 5q SMA and with one to three copies of the SMN2 gene, as well as for symptomatic patients two months of age and older with clinically diagnosed 5q SMA type 1 or type 2. For pre-symptomatic patients two months of age and older with 5q SMA with four copies of the SMN2 gene and for symptomatic patients with clinically diagnosed 5q SMA type 3, the G-BA considers a therapy according to the doctor's instructions of nusinersen or BSC to be an appropriate comparator therapy.

Change in the breakdown of patient populations:

After reviewing the submitted evidence, the G-BA divides patients with clinically diagnosed 5q SMA type 3 into 2 different sub-populations and uses the submitted study for one sub-population. Thus, the specific appropriate comparator therapy is specified separately for the respective sub-population on the basis of the patient characteristics. On the basis of the available evidence, no sufficient evidence can be derived for better or worse efficacy of nusinersen or BSC in certain SMA type 3 patients. Therefore, for the patients eligible for intrathecal application with nusinersen, therapy with nusinersen or BSC is the appropriate comparator therapy to the doctor's instructions. However, for patients for whom the administration of nusinersen is not an option due to the intrathecal form of administration, only best supportive care (BSC) represents the appropriate comparator therapy.

"Best supportive care" (BSC) is understood as the therapy that ensures the best possible, patient-individually optimised, supportive treatment to alleviate symptoms and improve quality of life. In this indication, various measures, including e.g. physiotherapy in accordance with the therapeutic products catalogue, may be suitable for treating the patient-individual symptomatology of spinal muscular atrophy, or appropriate ventilation of the patient, if this is necessary.

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

### 2.1.3 Extent and probability of the additional benefit

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

a) Patients 2 months of age and older with 5q spinal muscular atrophy (5q SMA) type 1

**Appropriate comparator therapy:**

Nusinersen

**Extent and probability of the additional benefit of risdiplam compared to nusinersen:**

Hint for a non-quantifiable additional benefit

b) Patients 2 months of age and older with 5q SMA type 2

**Appropriate comparator therapy:**

Nusinersen

**Extent and probability of the additional benefit of risdiplam compared to the appropriate comparator therapy:**

An additional benefit is not proven

c1) Patients 2 months of age and older with 5q SMA type 3 for whom intrathecal application of nusinersen is an option

**Appropriate comparator therapy:**

Treatment according to the doctor's instructions of nusinersen or BSC

**Extent and probability of the additional benefit of risdiplam compared to the appropriate comparator therapy:**

An additional benefit is not proven

c2) Patients 2 months of age and older with 5q SMA type 3 for whom intrathecal application of nusinersen is not an option

**Appropriate comparator therapy:**

Best supportive care (BSC)

**Extent and probability of the additional benefit of risdiplam compared to BSC:**

Hint for a non-quantifiable additional benefit

d1) Pre-symptomatic patients 2 months of age and older with 5q SMA and up to three copies of the SMN2 gene

**Appropriate comparator therapy:**

Nusinersen

**Extent and probability of the additional benefit of risdiplam compared to the appropriate comparator therapy:**

An additional benefit is not proven

d2) Pre-symptomatic patients 2 months of age and older with 5q SMA and four copies of the SMN2 gene

**Appropriate comparator therapy:**

Treatment according to the doctor's instructions of nusinersen or BSC

**Extent and probability of the additional benefit of risdiplam compared to the appropriate comparator therapy:**

An additional benefit is not proven

Justification:

A) Patients 2 months of age and older with 5q SMA type 1

For the present patient population, no randomised controlled trials (RCTs) were identified by the pharmaceutical company that allows a direct or an adjusted indirect comparison via a common bridge comparator versus the appropriate comparator therapy nusinersen.

The pharmaceutical company, therefore, submits individual arms from the FIREFISH and ENDEAR studies for a comparison between risdiplam and nusinersen. For nusinersen, the pharmaceutical company additionally identifies the RCT study EMBRACE and the 1-arm study CS3A, for risdiplam the 1-arm study JEWELFISH. However, these studies are not considered for a comparison of individual arms of different studies because either the populations do not match, the dosing scheme used is not in accordance with the nusinersen product information, or only pretreated patients were studied.

The FIREFISH study is an open-label one-arm study that enrolled patients with genetic evidence of 5q SMA and onset of clinical signs or symptoms from 28 days to ≤ 3 months of age, age between 1 month (28 days) and ≤ 7 months (210 days) at time of enrolment, and 2 SMN2 gene copies. Cohort 1 of the first part of the study is an exploratory dose-finding study with 4 patients. In cohort 2 of the first part of the study, 17 patients and in the second part of the study, 41 patients were examined. The planned treatment duration is 24 months, followed by an open extension phase of maximum of 3 years. The primary endpoint of the study was the percentage of patients who were able to sit without support after 12 months of treatment. Other patient-relevant endpoints included overall survival, other morbidity endpoints, and adverse events (AEs). In addition to oral treatment with risdiplam, the patients received supportive measures. Cohort 1 of the first part of the study is not considered for the present benefit assessment because the dosage of the patients deviates significantly from the product information. The first part of the study was launched in December 2016 and is being

conducted in 7 centres in Belgium, France, Italy, Switzerland and the USA. The second part of the study was launched in March 2018 and is being conducted in 14 centres in Brazil, China, Croatia, France, Italy, Japan, Poland, Russia, Turkey, Ukraine and the U.S.

The ENDEAR study is a double-blind RCT that included patients with genetically documented 5q SMA, age at the start of study ≤ 7 months, age at symptom onset between ≤ 6 months, and 2 SMN2 gene copies. In the study, 81 patients received treatment with nusinersen, and 41 patients received a sham intervention, each in addition to supportive measures equivalent to a BSC. Only the nusinersen arm is relevant for the comparison presented by the pharmaceutical company. Treatment with nusinersen was given as an intrathecal bolus injection on study days 1, 15, 29, 64 (saturation), and 183 and 302 (maintenance). The age-adjusted dosage deviated from the instructions given in the product information. However, the deviation from the product information has no overall influence on the present assessment. Due to the proof of the efficacy of nusinersen through positive effects for the endpoint achievement of motor milestones, the study was terminated before the end of the planned study duration (14 months). The median observation period to the final data cut-off was 280 days in the nusinersen arm. Coprimary endpoints of the study were the combined endpoint time to death or permanent ventilation and the percentage of patients who achieved motor milestones as measured by the Hammersmith Infant Neurological Examination (HINE) subscale 2. Patient-relevant secondary endpoints were overall survival, morbidity endpoints, and AEs. The study was conducted between July 2014 and December 2016 (final data cut-off) in 31 centres in Australia, Belgium, Germany, France, Great Britain, Italy, Japan, Canada, Korea, Sweden, Spain, Turkey and the USA.

After the last study visit, patients had the opportunity to participate in the SHINE study. The SHINE study is an open-label, long-term study of SMA patients who had previously participated in a study with nusinersen. Only the group of the SHINE study in which patients from the ENDEAR study were included (SHINE-ENDEAR) is relevant for the present research question.

For the comparison of individual arms of different studies, the pharmaceutical company uses for risdiplam the pooled population from cohort 2 of the first study part, as well as the second study part of the FIREFISH study (n = 58) and for nusinersen the data of the nusinersen arm of the ENDEAR study (n = 81).

During the written statement procedure, the pharmaceutical company submitted data comparing individual arms of the FIREFISH and ENDEAR studies with longer observation periods. For the FIREFISH study, the data cut-off 2 years after the inclusion of the last patient will be used; for the SHINE study, the data cut-off 27.08.2019 will be used.

For the comparison, the pharmaceutical company presents, on the one hand, a matching-adjusted-indirect comparison (MAIC) analysis without a bridge comparator and, on the other hand, an unadjusted comparison within the scope of a sensitivity analysis ("naïve" comparison). However, they do not use the "naive" comparison to derive the additional benefit.

*Comparability of the patient populations considered in the FIREFISH and ENDEAR studies*

The patient characteristics of the populations considered in the FIREFISH and ENDEAR studies are comparable with respect to the mean values for the characteristics age at screening, age at 1st dose, age at symptom onset, age at SMA diagnosis and disease duration, and SMN2 gene copy number. Regarding motor function measured by subscale 2 of the HINE and the CHOP-INTEND, there were only minor differences between the study populations at the start of the study. With regard to the geographical region, however, there are clear differences. As the inclusion criteria regarding medical care also differ between the studies and no information is available on the percentage of patients receiving physiotherapy, the influence of the conduction of the two studies in different countries remains unclear.

For further characteristics of symptomatology at the start of the study, such as hypotension, pneumonia or respiratory symptoms, data are only available for the ENDEAR study. A comparison of the populations considered in the FIREFISH and ENDEAR studies with regard to these characteristics is therefore not possible.

In addition, patients with awake non-invasive ventilation, invasive ventilation or tracheostomy were excluded from the FIREFISH study, as were certain patients with a history of respiratory failure or severe pneumonia or hospitalisation due to pulmonary events. No such exclusion criteria are found in the study protocol of the ENDEAR study.

Based on the exclusion criteria of the FIREFISH and ENDEAR studies, it can be summarised that the study population of the ENDEAR study has a poorer prognosis regarding respiratory events.

*Suitability of the indirect comparisons presented*

In the case of non-randomised comparisons without a bridge comparator, only those methods are generally considered useful for confounder adjustment that, in contrast to the matching-adjusted-indirect comparison (MAIC) analysis, are performed using the individual patient data. Furthermore, the pharmaceutical company does not provide sufficient justification for the variable selection in the MAIC analysis they conducted, so that outcome-based reporting cannot be ruled out. For the present benefit assessment, the "naive" comparison is considered.

Only those endpoints are considered for which there are clear effects, assuming comparable operationalisations.

Extent and probability of the additional benefit

Mortality

For the comparison of individual arms, all-cause mortality is not considered because no sufficiently large effects are shown that could not be based on systematic bias alone.

Morbidity

*Death or permanent ventilation*

The endpoint death or permanent ventilation is a combined endpoint of the individual components death and permanent ventilation, which are considered to be sufficiently similar in terms of their severity in the present indication. For the combined endpoint, the outcomes of time to death or time to permanent ventilation will be used.

In both the FIREFISH (risdiplam) and ENDEAR (nusinersen) studies, permanent ventilation was defined as ventilation ≥ 16 hours per day continuously for > 21 days in the absence of acute reversible events or tracheostomy. Despite differences in the concretisation of ventilation, the endpoint operationalisation of both studies is sufficiently comparable.

For the combined endpoint death or permanent ventilation as well as for the single component permanent ventilation, a clear statistically significant difference to the advantage of risdiplam compared to nusinersen is shown on the basis of the comparison of individual arms of the studies FIREFISH and ENDEAR.

*Permanent ventilation*

For the single component, permanent ventilation of the combined endpoint, a clear statistically significant difference to the advantage of risdiplam compared to nusinersen is shown on the basis of the "naive" comparison of individual arms of the studies FIREFISH and ENDEAR.

Table 1: Comparison of individual arms of different studies (unadjusted): Risdiplam (FIREFISH) vs nusinersen (SHINE-ENDEAR)

| Endpoint | Risdiplam (Study FIREFISH Part 1, cohort 2 + part 2) [a] | | Nusinersen (SHINE-ENDEAR study) [b] | | Risdiplam vs Nusinersen |
|---|---|---|---|---|---|
| | N | Median time to event in months [95%-CI]<br>*Patients with event n (%)* | N | Median time to event in months [95%-CI]<br>*Patients with event n (%)* | HR [95%-CI][c]; p-value |
| Death or permanent ventilation[d] | 58 | n.d.<br>*9 (15.5)* | 81 | n.d.<br>*40 (49.4)* | 0.24 [0.09; 0.44]; no data available |
| Permanent ventilation | 58 | n.d.<br>*4 (6.9)* | 81 | n.d.<br>*24 (29.6)* | 0.18 [0.04; 0.40]; no data available |

a. Data cut-off 2 years after inclusion of the last patient
b. Data cut-off of 27.08.2019:
c. HR and CI based on unstratified Cox model
d. Combined endpoint consisting of the individual components of death and permanent ventilation (defined as ventilation ≥ 16 hours per day continuously for > 21 days in the absence of acute reversible events or tracheostomy);

HR: hazard ratio; n. d.: no data available; CI: confidence interval; N: number of patients evaluated; n: number of patients with event

*Other morbidity endpoints*

For the comparison of individual arms, motor functioning (CHOP-INTEND) and achievement of motor milestones (HINE subscale 2) will not be considered, as no sufficiently large effects that could not be based on systematic bias alone are shown. Furthermore, based on the information provided by the pharmaceutical company, it is unclear how or whether an adjustment was made for the different observation durations of the two studies for binary and continuous endpoints, respectively.

Quality of life

Health-related quality of life was not assessed in either study.

Side effects

The endpoints serious adverse events (SAEs) and discontinuation due to adverse events (AEs) are not considered for the comparison of individual arms, as there is no comparison of SAEs and discontinuations due to AEs of the FIREFISH study with the ENDEAR study without considering disease-related events.

Serious respiratory events are a significant patient-relevant endpoint in the present indication. However, the pharmaceutical company does not provide a comparison for this endpoint.

Overall assessment

The "naive" comparison presented is associated with very large uncertainties. The "naïve" comparison of individual arms of the FIREFISH and ENDEAR studies comparing risdiplam, and nusinersen shows a clear statistically significant effect to the advantage of risdiplam for the endpoints death or permanent ventilation as well as the single component permanent ventilation. However, on the basis of the present "naïve" comparison, it cannot be safely excluded that these effects are solely due to a systematic bias caused by confounding variables, as it can be assumed, in particular on the basis of the exclusion criteria of the FIREFISH and ENDEAR studies, that the study population of the ENDEAR study has a poorer prognosis with regard to respiratory events.

The data presented are therefore difficult to interpret. However, the observed differences for time to permanent ventilation or the combined endpoint of time to death or time to permanent ventilation suggest that risdiplam is at least not inferior to nusinersen.

In addition, oral administration of risdiplam is thought to have a noticeable advantage over intrathecal administration of nusinersen, especially in younger children. Intrathecal injection is associated with common side effects such as headache, vomiting and back pain, but occasionally serious infections or hypersensitivity reactions have been reported. Furthermore, intrathecal injections often require anaesthesia or sedation of the patients, which are associated with additional risks in the present therapeutic indication.

In summary, taking into account the assumed non-inferiority of risdiplam for the treatment of patients 2 months of age and older with 5q SMA type 1 based on data from a comparison of individual arms from different studies ("naïve comparison"), an expected advantage of oral administration over intrathecal injection, and taking particular account of the severity of the disease, there is a hint of an additional benefit compared with nusinersen, the extent is non-quantifiable due to the limited evidence available.

b) Patients 2 months of age and older with 5q SMA type 2

Due to the lack of directly comparable studies, the pharmaceutical company is examining the possibility of an adjusted indirect comparison for the evaluation of the additional benefit of risdiplam compared to the appropriate comparator therapy nusinersen.

For risdiplam, the pharmaceutical company considers the sub-population of the RCT SUNFISH study relevant for the research question, in which non-ambulatory patients with clinical symptoms of SMA type 2 or 3 received either risdiplam or placebo.
For comparison against nusinersen, the pharmaceutical company identifies the CHERISH and EMBRACE studies. The CHERISH study is an RCT in which patients with type 2 SMA were treated with either nusinersen or a sham intervention. The EMBRACE RCT included patients with genetically documented 5q SMA who received either nusinersen or a sham intervention.

However, when examining the similarity of the studies, the pharmaceutical company finds significant differences, in particular with regard to the age at the time of screening of the included patients as well as their duration of disease, and concludes that comparability between the studies is not given.
In summary, an adjusted indirect comparison of risdiplam versus the appropriate comparator therapy for patients with SMA type 2 is not possible based on the identified studies.
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 therapeutic option for patients 2 month of age and older with 5q SMA type 2.

c) Patients 2 months of age and older with 5q SMA type 3

For the assessment of the additional benefit of risdiplam compared to the appropriate comparator therapy, the pharmaceutical company uses the SUNFISH study.

The second part of the SUNFISH study is a double-blind RCT that included non-ambulatory patients with a genetically confirmed diagnosis of 5q SMA and an age range of 2 to 25 years at screening, as well as clinical symptoms of type 2 or 3 SMA. In this study, non-ambulation was defined by the patient's inability to walk ≥ 10 m without support. 120 patients received treatment with risdiplam, 60 patients received placebo in each case in addition to supportive measures. The duration of treatment is 12 months, followed by 12 months of active treatment with risdiplam and 3 years of open-label follow-up treatment with risdiplam.
The primary endpoint of the study was to demonstrate the change in the total score of the Motor Function Measure - 32 items (MFM-32) at month 12. Secondary endpoints were morbidity and adverse events (AEs).
The SUNFISH study (part 2) was launched in October 2017 and is ongoing. It is conducted in 42 test centres in Belgium, Brazil, Canada, China, Croatia, France, Italy, Japan, Poland, Russia, Serbia, Spain, Turkey and the USA.

The concomitant medicinal and non-medical measures used in the SUNFISH study can be regarded as sufficient implementation of therapy in the sense of a BSC according to the recommendations in SMA.

During the written comments procedure, the clinical experts made it clear that there are some patients for whom the intrathecal application of nusinersen is not possible, for example, due to pronounced scoliosis or spinal stiffness, or who do not decide to undergo nusinersen therapy due to a technically difficult or only CT-guided intrathecal application of nusinersen and the associated risks. According to the estimation of the clinical experts, the percentage of these patients is about 15% of patients with 5q SMA type 3.

Taking into account the comments of the clinical experts, two sub-populations can be identified in the context of the intended comparator therapy for patients with 5q SMA type 3, therapy that chooses between nusinersen or BSC according to doctor's instructions. On the one hand, there is a sub-population for which intrathecal application of nusinersen is an

option. In contrast, there is a sub-population of patients for whom nusinersen is not an option due to intrathecal application.

Accordingly, a division is made into the following sub-populations:

c1: Patients 2 months of age and older with 5q SMA type 3 for whom intrathecal application of nusinersen is an option:

A comparison with BSC alone is generally not sufficient for the appropriate comparator therapy defined by the G-BA, consisting of therapy with nusinersen or BSC according to the doctor's instructions. An adequate implementation of the appropriate comparator therapy would be possible if treatment with nusinersen was not an option for the patients included in the study. However, based on the available information, it can be assumed that nusinersen would have been an approved and fundamentally suitable therapeutic option for a relevant percentage of the patients with 5q SMA type 3 included in the study.
The SUNFISH study is therefore not suitable for deriving conclusions on the additional benefit of risdiplam compared to the appropriate comparator therapy for the present sub-population with SMA type 3.
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 therapeutic option for the present sub-population of patients 2 months of age and older with 5q SMA type 3.

c2: Patients 2 months of age and older with 5q SMA type 3 for whom intrathecal application of nusinersen is not an option:

For patients for whom nusinersen is not an option due to intrathecal application, only BSC is considered as an appropriate comparator therapy. For this sub-population, the results of patients with clinically diagnosed SMA type 3 from the SUNFISH study can be used.

Extent and probability of the additional benefit

Mortality

No deaths occurred in the sub-population with SMA type 3 until month 12.

Morbidity

*MFM-32 (gross and fine motor skills)*

The MFM-32 examines motor function specifically in patients with neuromuscular diseases, including SMA. The instrument includes 32 test items that assess physical function in 3 domains (standing transfers and ambulation; proximal and axial function; distal function). The test items are each scored on a 4-point Likert scale ranging from 0 (the task cannot be started)

to 3 (the task is performed fully and "normally). The sum of the scores is transferred to a scale from 0 to 100, with higher scores indicating better motor skills.

The pharmaceutical company submits results for the total score in the form of mean differences and of responder analyses (patients with an improvement of the MFM-32-total score by ≥ 3 or ≥ 0 points). In the benefit assessment, the results for the total score are presented in the form of the mean differences. The responder analyses submitted by the pharmaceutical company are not presented because the MFM-32 is a complex scale, and the response criteria chosen do not represent at least 15% of the scale range of the instrument.

For mean change, there was no statistically significant difference between treatment groups considering at month 12.

*Hammersmith Functional Motor Scale Expanded – HFMSE*

The HFMSE can be used to assess motor skills in patients 2 years of age and older with SMA types 2 and 3. The instrument comprises 33 test items and operationalises mainly gross motor functions (changing position while lying down, crawling, rising from kneeling position, standing, walking and jumping). The test items are each scored on a three-point scale from 0 (is unable to) to 2 (is able to without help), resulting in a maximum score of 66. Higher values mean better motor functionality.

The pharmaceutical company presents results in the form of mean differences and responder analyses (patients with an improvement in the HFMSE total score of ≥ 2 or ≥ 0 points). The responder analyses submitted by the pharmaceutical company are not presented because the HFMSE is a complex scale, and the response criteria chosen do not represent at least 15% of the scale range of the instrument.

For mean change, there was no statistically significant difference between treatment groups considering at month 12.

*Revised Upper Limb Module - RULM*

The RULM is an instrument for the examination of motor function of the upper extremities in patients with SMA type 2 and 3. Validity and reliability were demonstrated. The instrument includes 19 items for testing proximal and distal motor functions of the arms and hands and an input item for classifying functionality. 18 of the 19 test items are scored on a three-point scale from 0 (is unable) to 2 (is able without difficulty), and 1 test item is scored on a two-point scale, resulting in a maximum score of 37. A higher total score corresponds to a better functional status.

The pharmaceutical company presents results in the form of mean differences and responder analyses. The responder analyses submitted by the pharmaceutical company are not presented because the RULM is a complex scale, and the response criteria chosen do not represent at least 15% of the scale range of the instrument.

For the mean change, there is a statistically significant difference for the benefit of risdiplam + BSC versus placebo + BSC. In order to assess the relevance of the results, the standardised mean difference in terms of Hedges' g is considered. The 95% confidence interval is completely above the irrelevance threshold of 0.2. This is interpreted as a relevant effect.

*SMA Independence Scale (SMAIS)*

According to the pharmaceutical company, the SMAIS was developed specifically for use in patients with SMA types 2 and 3 to assess functional independence. It contains 29 test items that assess how much assistance is needed from another person to perform activities of daily living within the past 7 days. Since the pharmaceutical company does not provide validation for the SMAIS and several other and validated morbidity instruments were used in the study, additional consideration of the SMAIS is not provided.

*Health status (EQ-5D VAS)*

The Visual Analogue Scale (VAS) was completed only by patients ≥ 12 years of age. For mean change, there was no statistically significant difference between treatment groups considering at month 12.

Quality of life

Health-related quality of life was not assessed.

Side effects

When recording serious adverse events (SAEs), events were also recorded that are part of the symptomatology of the underlying disease or events that can be both a side effect and symptomatology of the underlying disease. Since evaluations without events attributable to the underlying disease are relevant for the benefit assessment, the results on SAEs are not presented. No discontinuations due to AEs occurred until month 12. For the specific AE skin and subcutaneous tissue disorders (SOC, AEs), there is a statistically significant difference at month 12 to the disadvantage of risdiplam versus BSC. Overall, neither an advantage nor a disadvantage for risdiplam compared to BSC is derived in the category of side effects.

Overall assessment / conclusion

For patients 2 months of age and older with 5q SMA type 3, for whom intrathecal application of nusinersen is not an option, the results of patients with clinically diagnosed SMA type 3 are used from the SUNFISH study. This is a small sub-population of patients with 5q SMA type 3 for whom intrathecal application of nusinersen is not possible or who choose not to receive nusinersen therapy due to the risks of intrathecal application. For these, only the comparator BSC used in the SUNFISH study can be considered as an appropriate comparator therapy.

For mortality and the MFM-32, HFMSE and EQ-5D VAS endpoints in the morbidity category, there were no significant differences between the treatment arms. For the endpoint RULM of the morbidity category, there was a statistically significant difference in the benefit of

risdiplam compared to BSC, which is interpreted as a relevant effect. Health-related quality of life was not assessed.

In the category of side effects, the results on SAEs are not included, as there are no evaluations without events attributable to the underlying disease. No discontinuations due to AEs occurred in the sub-population until month 12. Overall, neither an advantage nor a disadvantage is derived for risdiplam compared to BSC in the category of side effects.

The available data are subject to very large uncertainties since results for the total population of patients 2 months of age and older with 5q SMA type 3 from the SUNFISH study are used as a makeshift for the comparatively small group of patients 2 months of age and older with 5q SMA type 3 for whom intrathecal application of nusinersen is not an option

In summary, there is a hint of an additional benefit for risdiplam for the treatment of patients 2 months of age and older with 5q SMA type 3 for whom intrathecal application of nusinersen is not an option, taking into account the benefit in motor function of the upper extremities (RULM) shown in the SUNFISH study, compared to the appropriate comparator therapy BSC, although the extent of this benefit is non-quantifiable due to the large uncertainties in the study data used.

(d) Pre-symptomatic patients 2 months of age and older with 5q SMA with one to four copies of the SMN2 gene

The definition of the appropriate comparator therapy results in 2 different patient populations for pre-symptomatic patients with SMA 2 months of age and older depending on the number of existing SMN2 gene copies. It is assumed that patients with only 1 SMN2 gene copy are already prenatally or at birth severely symptomatic and consequently not included in the patient population of pre-symptomatic patients.

d1) Pre-symptomatic patients 2 months of age and older with 5q SMA and up to three copies of the SMN2 gene

No data are available for the assessment of the additional benefit of risdiplam compared with the appropriate comparator therapy nusinersen in pre-symptomatic patients 2 months of age and older with 5q SMA and up to three copies of the SMN2 gene. 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 therapeutic option for pre-symptomatic patients 2 month of age and older with 5q SMA and up to three copies of the SMN2 gene.

d2) Pre-symptomatic patients 2 months of age and older with 5q SMA and four copies of the SMN2 gene

No data are available for the assessment of the additional benefit of risdiplam compared with the appropriate comparator therapy "therapy with nusinersen or BSC according to the doctor's instructions "in pre-symptomatic patients 2 months of age and older with 5q SMA and up four copies of the SMN2 gene. 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 therapeutic option for pre-symptomatic patients 2 month of age older with 5q SMA and four copies of the SMN2 gene.

### 2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product "Evrysdi" with the active ingredient risdiplam, which was approved as an orphan drug. However, the pharmaceutical company has irrevocably notified the G-BA that, despite the orphan drug status for risdiplam, a regular benefit assessment compared to the appropriate comparator therapy is to be conducted. Risdiplam is approved for the treatment of 5q spinal muscular atrophy in patients 2 months of age and older, with 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, 5 patient groups were distinguished.

*a) Patients 2 months of age and older with 5q SMA type 1:*
The G-BA determined nusinersen as appropriate comparator therapy. The pharmaceutical company submits individual arms from the FIREFISH (1-arm study with risdiplam) and ENDEAR (RCT with nusinersen) studies for a comparison between risdiplam and nusinersen. The patient characteristics of the populations considered in the FIREFISH and ENDEAR studies are comparable with respect to certain characteristics of patient age and disease duration. However, based on the exclusion criteria of the studies, it can be assumed that the study population of the ENDEAR study has a poorer prognosis regarding respiratory events. Since the matching-adjusted-indirect comparison (MAIC) analysis presented by the company is not suitable, the "naive" comparison is considered here. For the endpoints death or permanent ventilation as well as the single component permanent ventilation, there is a clearly statistically significant effect in favour of risdiplam. The data presented are difficult to interpret due to the large uncertainties of the comparison. However, the observed differences suggest that risdiplam is at least not inferior to Nusinersen. In addition, oral administration of risdiplam is thought to have a noticeable advantage over intrathecal administration of nusinersen, especially in younger children.

In summary, taking into account the assumed non-inferiority of risdiplam for the treatment of patients 2 months of age and older with 5q SMA type 1 based on data from a comparison of individual arms from different studies ("naïve comparison"), an expected advantage of oral administration over intrathecal injection, and taking particular account of the severity of the disease, there is a hint of an additional benefit compared with nusinersen, the extent is non-quantifiable due to the limited evidence available.

*b) Patients 2 months of age and older with 5q SMA type 2*

The G-BA determined nusinersen as appropriate comparator therapy. For risdiplam, the pharmaceutical company considers the sub-population of the RCT SUNFISH study relevant for the research question, in which non-ambulatory patients with clinical symptoms of SMA type 2 or 3 received either risdiplam or placebo. For comparison against nusinersen, the pharmaceutical company identifies the CHERISH and EMBRACE studies. However, when examining the similarity of the studies, the pharmaceutical company finds significant differences, in particular with regard to age and duration of disease, and concludes that there is no comparability between the studies.

In summary, based on the identified studies, an adjusted indirect comparison of risdiplam versus nusinersen for patients with SMA type 2 is not possible. 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 therapeutic option for patients 2 month of age and older with 5q SMA type 2.

*c) Patients 2 months of age and older with 5q SMA type 3*

The G-BA determined the appropriate comparator therapy to be a therapy according to the doctor's instructions of nusinersen or BSC.
For the evaluation of the additional benefit of risdiplam compared to the appropriate comparator therapy, the pharmaceutical company uses the placebo-controlled SUNFISH study.

The concomitant medicinal and non-medical measures used in the study can be regarded as sufficient implementation of a BSC therapy. During the written comments procedure, the clinical experts made it clear that intrathecal injection with nusinersen is not an option for approximately 15% of patients with 5q SMA type 3 due to, for example, pronounced scoliosis or the associated risk.

It is divided into the following sub-populations:

*c1: Patients 2 months of age and older with 5q SMA type 3 for whom intrathecal application of nusinersen is an option:*

For patients eligible for the intrathecal application of nusinersen, the additional benefit is not proven, as no study was submitted by the pharmaceutical company that would have been suitable for an assessment of the additional benefit compared to the appropriate comparator therapy, that consists of therapy with the selection of nusinersen or BSC according to doctor's instructions.

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 therapeutic option for the present sub-population of patients 2 months of age and older with 5q SMA type 3.

*c2: Patients 2 months of age and older with 5q SMA type 3 for whom intrathecal application of nusinersen is not an option:*

Since only BSC can be considered as an appropriate comparator therapy for this sub-population, the data of patients with clinically diagnosed SMA type 3 from the SUNFISH study will be considered for them.

There were no significant differences in mortality and in morbidity; there was only a statistically significant and relevant difference in the advantage of risdiplam over BSC regarding the motor function of the upper extremities. Health-related quality of life was not assessed. In the category of side effects, there was neither an advantage nor a disadvantage for Risdiplam compared to BSC.

Due to the transfer of results from the total population of patients with 5q SMA type 3 from the SUNFISH study to the comparatively small group of patients with 5q SMA type 3, for whom intrathecal application of nusinersen is not an option, the available data are subject to very large uncertainties.

In summary, taking into account the benefit shown for motor function of the upper extremities, there is a hint of an additional benefit for risdiplam over BSC for the treatment of patients 2 months of age and older with 5q SMA type 3 for whom intrathecal application of nusinersen is not an option, although the extent of this benefit is non-quantifiable due to the large uncertainties in the study data used.

*d1) Pre-symptomatic patients 2 months of age and older with 5q SMA and up to three copies of the SMN2 gene*

The G-BA determined nusinersen as appropriate comparator therapy. No data are available for the assessment of the additional benefit 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 therapeutic option for pre-symptomatic patients 2 month of age and older with 5q SMA and up to three copies of the SMN2 gene.

*d2) Pre-symptomatic patients 2 months of age and older with 5q SMA and four copies of the SMN2 gene*

The G-BA determined the appropriate comparator therapy to be a therapy according to doctor's instructions of nusinersen or BSC. No data are available for the assessment of the additional benefit 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 therapeutic option for pre-symptomatic patients 2 months of age older with 5q SMA and four copies of the SMN2 gene.

## 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. Overall, the estimated number of prevalent patients reported by the pharmaceutical company is higher than in the previous procedure. This is due to the different sources and ways of deriving the prevalence. Whereas in the previous procedure, the prevalence for the year 2007 was taken directly from one source, in the present dossier, the pharmaceutical company derives the prevalence via incidence and disease duration separately by SMA types using several sources. Due to the longer average duration of the disease and a correspondingly higher number of prevalent cases, the relatively high percentage of patients with later disease onset (SMA type 2 and SMA type 3) is particularly significant.

In order to account for the uncertainties of the different derivation pathways, a wider range of data from the present dossier and the previous procedure is submitted in the present resolution for patients with SMA type 1 and for the group of patients 2 months of age and older with 5q SMA type 2 or with 5q SMA type 3. The slight variations in the target populations due to the therapeutic indications can be neglected, as it is assumed that these are represented with a wide range.

A reliable indication of the number of SHI patients for the group of pre-symptomatic patients with 5q SMA is currently not possible. This is justified subsequently:
Based on an incidence between 1:6,000 to 1:11,000 in newborns[2] based on the total population of SMA patients in Germany, a hint for the number of pre-symptomatic patients could be derived. However, this approach is subject to great uncertainty, as it can be assumed that only very few pre-symptomatic patients have been identified in Germany to date. A diagnosis before symptom onset was probably made mainly on the basis of positive family history and accordingly covered only a small percentage of the total population of SMA patients in Germany. However, the number of patients diagnosed before and after symptom onset is expected to change in the future, as SMA has been introduced into general newborn screening in Germany in 2021.

Since it can be assumed that newborn screening for 5q SMA has a relevant influence on the number of pre-symptomatically diagnosed patients in Germany, in the sense of an expected increase, the present resolution refrains from stating the number of SHI patients for the group of pre-symptomatic patients with 5q SMA.

[2] Children's Policy: Newborn screening for 5q spinal muscular atrophy, resolution of 17.12.2020

## 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: 28 June 2021):
https://www.ema.europa.eu/en/documents/product-information/evrysdi-epar-product-information_en.pdf

Treatment with risdiplam should only 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 contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 September 2021).

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 is patient-individual 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 dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" for under 1-year-old children (7.6 kg body weight) and adults (77 kg) were used. [3]

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

Treatment period:

| Designation of the therapy | Treatment mode | Number of treatments/ patient/ year | Treatment duration/ treatment (days) | Days of treatment/ patient/ year |
|---|---|---|---|---|
| Medicinal product to be assessed | | | | |
| Risdiplam | 1 x daily | 365 | 1 | 365 |
| Patient group c1, c2 and d2 | | | | |
| Best supportive care | patient-individual | | | |
| Appropriate comparator therapy | | | | |
| Patient groups a, b and d1 | | | | |
| Nusinersen 1st year | Day 0, 14, 28, 63, after that every four months | 6.5 | 1 | 6.5 |
| Nusinersen Subsequent years | every 4 months | 3 | 1 | 3 |
| Patient groups c1 and d2 | | | | |
| Nusinersen 1st year | Day 0, 14, 28, 63, after that every four months | 6.5 | 1 | 6.5 |
| Nusinersen Subsequent years | every 4 months | 3 | 1 | 3 |
| Best supportive care | patient-individual | | | |
| Patient group c2) | | | | |

| Designation of the therapy | Treatment mode | Number of treatments/ patient/ year | Treatment duration/ treatment (days) | Days of treatment/ patient/ year |
|---|---|---|---|---|
| Best supportive care | patient-individual | | | |

Consumption:

| Designation of the therapy | Dosage/ application | Dosage/ patient/ treatment days | Usage by potency/ treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | |
| Risdiplam | 0.2 mg/kg = 1.52 mg -<br>5 mg | 1.5 mg -<br>5 mg | 1 x 1.5 mg -<br>1 x 5 mg | 365 | 547.5 mg -<br>1,825 mg |
| Patient groups c1, 2 and d2 | | | | | |
| Best supportive care | patient-individual | | | | |
| Appropriate comparator therapy | | | | | |
| Patient groups a, b and d1 | | | | | |
| Nusinersen 1st year | 12 mg | 12 mg | 1 x 12 mg | 6.5 | 6.5 x 12 mg |
| Nusinersen Subsequent years | 12 mg | 12 mg | 1 x 12 mg | 3 | 3 x 12 mg |
| Patient groups c1 and d2 | | | | | |
| Nusinersen 1st year | 12 mg | 12 mg | 1 x 12 mg | 6.5 | 6.5 x 12 mg |
| Nusinersen Subsequent years | 12 mg | 12 mg | 1 x 12 mg | 3 | 3 x 12 mg |
| Best supportive care | patient-individual | | | | |
| Patient group c2) | | | | | |

| Designation of the therapy | Dosage/ application | Dosage/ patient/ treatment days | Usage by potency/ treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| Best supportive care | patient-individual | | | | |

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. The required number of packs of a particular potency was first determined based on consumption to calculate the annual treatment costs. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

**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 POS | € 10,943.06 | € 1.77 | € 621.68 | € 10,319.61 |
| Patient group c1, c2 and d2 | | | | | |
| Best supportive care | patient-individual | | | | |
| Appropriate comparator therapy | | | | | |
| Nusinersen 12 mg | 1 SFI | € 92,473.94 | € 1.77 | € 5,280.63 | € 87,191.54 |
| Best supportive care | patient-individual | | | | |
| Abbreviations: SFI = solution for injection; POS = powder for preparation of an oral solution | | | | | |

LAUER-TAXE® last revised: 15 September 2021

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 standard expenditure in the course of the treatment are not shown.

Additionally, required SHI services for the application of 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 assessment 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 |
|---|---|---|---|
| 1st year | non-quantifiable | 6.5 | non-quantifiable |
| Subsequent years | non-quantifiable | 3 | non-quantifiable |

## 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 20 September 2016, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

The appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 27 April 2021.

On 23 April 2021, 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 1, sentence 2 VerfO.

By letter dated 30 April 2021 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 29 July 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 2 August 2021. The deadline for submitting written statements was 23 August 2021.

The oral hearing was held on 6 September 2021.

By letter dated 7 September 2021, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addenda prepared by IQWiG was submitted to the G-BA on 1 October 2021.

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 12 October 2021, and the proposed resolution was approved.

At its session on 21 October 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

### Chronological course of consultation

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee Medicinal product | 20 September 2016 | Determination of the appropriate comparator therapy |
| Subcommittee Medicinal product | 27 April 2021 | New determination of the appropriate comparator therapy |
| Working group Section 35a | 31 August 2021 | Information on written statements received; preparation of the oral hearing |
| Subcommittee Medicinal product | 6 September 2021 | Conduct of the oral hearing,<br>Commissioning of the IQWiG with the supplementary assessment of documents |
| Working group Section 35a | 14 September 2021<br>21 September 2021<br>05 October 2021 | Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure |
| Subcommittee Medicinal product | 12 October 2021 | Concluding discussion of the draft resolution |
| Plenum | 21 October 2021 | Adoption of the resolution on the amendment of Annex XII AM-RL |

Berlin, 21 October 2021

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

Prof. Hecken