Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive: Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V: Risdiplam (spinal muscular atrophy)

of 21 October 2021

At its session on 21 October 2021, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as amended by the publication of the resolution of D. month YYYY (BAnz AT TT.MM.JJJJ BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient risdiplam as follows:

Risdiplam

Resolution of: 21 October 2021
Entry into force on: 21 October 2021
BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 26 March 2021):

"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 of 21 October 2021):

Therapeutic indication according to marketing authorisation

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

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

Study results according to endpoints: [1]

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary

[1] Data from the dossier assessment of the IQWiG (A21-50) and from the addendum (A21-118), unless otherwise indicated.

Mortality	↔	No relevant difference
Morbidity	↔	Non-inferiority considering data from a comparison of individual arms from different studies
Health-related quality of life	∅	No data available
Side effects	↑	expected advantage of oral administration over intrathecal injection

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	No data available
Morbidity	∅	No data available
Health-related quality of life	∅	No data available
Side effects	∅	No data available

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	There are no assessable data.
Morbidity	n.a.	There are no assessable data.

Health-related quality of life	∅	No data available
Side effects	n.a.	There are no assessable data.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant difference
Morbidity	↑	Advantage in upper extremity motor function considering results for the total population of patients with 5q SMA type 3
Health-related quality of life	∅	No data available
Side effects	↔	Overall, no relevant differences.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

SUNFISH RCT study (data cut-off 06.09.2019[2]): Risdiplam + BSC **vs** placebo + BSC sub-population: Patients with clinically diagnosed SMA type 3

[2] The first 12 months of randomised treatment were included in the analysis for each patient.

Mortality

Endpoint	Risdiplam + BSC		Placebo + BSC		Risdiplam + BSC vs placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	[95%-CI]; p-value
Overall mortality[a]	36	0 (0)	16	0 (0)	–

Morbidity

Endpoint	Risdiplam + BSC			Placebo + BSC			Risdiplam + BSC vs placebo + BSC
	N[b]	Values at start of study MV (SD)	Change to month 12 MV[g] (SD)	N[b]	Values at start of study MV (SD)	Change to month 12 MV[g] (SD)	MD [95 %-CI]; p-value[c]
Gross and fine motor skills (MFM-32)[d, e]	35	54.4 (9.6)	0.9 (0.5)	14	55.1 (9.6)	0.6 (0.7)	1.48 [-0.29; 3.24]; n.d.
Motor function of the upper extremities (RULM)[f]	34	25.6 (6.6)	1.7 (0.4)	15	25.3 (7.1)	-0.5 (0.6)	2.19 [0.71; 3.67]; n.d. Hedges' g: 0.91 [0.28; 1.53]
Functional motor abilities (HFMSE)[g]	34	25.5 (12.8)	0.2 (0.6)	15	24.8 (13.5)	-0.7 (0.9)	0.89 [-1.30; 3.07]; n.d.
Health status (EQ-5D VAS)[h, i]	21	74.5 (20.9)	4.3 (2.8)	8	72.5 (22.2)	2.1 (4.3)	2.17 [-8.33; 12.66]; n.d.

Health-related quality of life

Health-related quality of life was not collected in the study.

Side effects

Endpoint	Risdiplam + BSC		Placebo + BSC		Risdiplam + BSC vs placebo + BSC
	N	Patients with event n (%)	N	Patients with event n (%)	[95%-CI]; p-value
AEs (presented additionally)	36	33 (91.7)	16	15 (93.8)	–
SAEs	no usable data available[j]				
Discontinuation because of AEs	36	0 (0)	16	0 (0)	–
Skin and subcutaneous tissue disorders (SOC, AEs)	36	8 (22.2)	16	0 (0)	–; 0,044[k]

a. Operationalised via the grade 5 AEs (AEs that lead to death) that occurred in the study
b. The number of patients who were taken into account in the evaluation for calculating the effect estimate; the values at the start of the study (possibly at other times) can be based on other patient numbers.
c. MMRM with age (stratification variable), baseline, visit as independent variables, and interaction between treatment and visit as well as baseline and visit
d. Higher scores mean better motor function; positive effects (risdiplam minus placebo) mean an advantage for risdiplam. Scale range: 0 to 100 points. For the individual domains D1, D2, D3, the pharmaceutical company does not present separate evaluations
e. Effect estimate according to "Treatment Policy Estimand" (main analysis of the pharmaceutical company): Analyses based on this estimand ignore the occurrence of intercurrent events, in this case, the use of prohibited concomitant medication (affecting 1 patient in the study who was treated with nusinersen [30]). The analysis excluding this patient ("hypothetical strategy estimand") does not differ from the main analysis of the pharmaceutical company.
f. Higher scores mean better motor function; positive effects (risdiplam minus placebo) mean an advantage for the intervention. Scale range: 0 to 37 points
g. Higher scores mean better motor function; positive effects (risdiplam minus placebo) mean an advantage for the intervention. Scale range: 0 to 66 points
h. completed by patients ≥ 12 years of age. Higher (increasing) values mean better health status; positive effects (risdiplam minus placebo) mean an advantage for risdiplam. Scale range: 0 to 100 points
i. The responder analyses submitted by the pharmaceutical company regarding the EQ-5D VAS with a response criterion of 10 points are presented additionally in the appendix C.2 of IQWiG's benefit assessment
j. Relevant percentage of events of the underlying disease or events that can be both side effects and symptomatology of the underlying disease (e.g. oxygen saturation decreased, sleep apnoea syndrome)
k. Own calculation, unconditional exact test (CSZ method according to Martín Andrés & Silva Mato,1994). No presentation of effect estimate and CIs, as not informative

BSC: Best supportive care; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; G-BA: Federal Joint Committee; HFSME: Hammersmith Functional Motor Scale – expanded; n. d.: no data; CI: confidence interval; MD: Mean difference; MFM-32: Motor Function Measure - 32 Items; MMRM: mixed model for repeated measures; MV: mean value; pU: pharmaceutical company; RCT: randomised controlled trial; RULM: Upper Limb Module Test (revised version); SD: Standard deviation; SMA: spinal muscular atrophy; VAS: visual analogue scale

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	No data available
Morbidity	∅	No data available
Health-related quality of life	∅	No data available
Side effects	∅	No data available
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	∅	No data available
Morbidity	∅	No data available
Health-related quality of life	∅	No data available
Side effects	∅	No data available
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

2. Number of patients or demarcation of patient groups eligible for treatment

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

approx. 110 – 300 patients

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

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

approx. 880 – 1840 patients

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

No specification possible

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.

4. Treatment costs

Annual treatment costs:

Patient groups a, b and d1

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Risdiplam	€ 94,166.44 - € 313,888.14
Appropriate comparator therapy:	
Nusinersen 1st year	€ 566,745.01
additionally required SHI services	non-quantifiable
Nusinersen subsequent years	€ 261,574.62
additionally required SHI services	non-quantifiable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 September 2021)

Patient groups c1 and d2

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Risdiplam	€ 94,166.44 - € 313,888.14
Best supportive care	patient-individual
Appropriate comparator therapy:	
Nusinersen 1st year	€ 566,745.01
additionally required SHI services	non-quantifiable
Nusinersen subsequent years	€ 261,574.62
additionally required SHI services	non-quantifiable
Best supportive care	patient-individual

Patient group c2)

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Risdiplam	€ 94,166.44 - € 313,888.14
Best supportive care	patient-individual
Appropriate comparator therapy:	
Best supportive care	patient-individual

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 September 2021)

II. The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 21 October 2021.

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

Berlin, 21 October 2021

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

Prof. Hecken