Risdiplam (spinal muscular atrophy)

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Requirement of routine practice data collection and evaluations according to Section 35a, paragraph 3b, sentence 1 SGB V for the active ingredient risdiplam:

At the time of entry into force of this resolution, the approved therapeutic indications according to the product information is as follows:

> 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.

The pharmaceutical company has submitted an application for an extension of the therapeutic indication. After extension of the therapeutic indication, the therapeutic indication of risdiplam shall be as follows:

> 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.

The resolution is based on the use of the active ingredient risdiplam in the treatment of patients according to the extension of the therapeutic indication.

1. Requirements for routine practice data collection and evaluations

The justification for the requirement of routine practice data collection for the active ingredient risdiplam for the purpose of the benefit assessment results from the procedure-initiating resolution on the requirement of routine practice data collection of 7 October 2021 as well as from the expected extension of the therapeutic indications of risdiplam. Accordingly, the G-BA extends the therapeutic indication of the resolution on the requirement of routine practice data collection and evaluations also to include patients aged 0 to 2 months.

Should the expected extension of the therapeutic indication for risdiplam not be approved or be approved in a modified form, the G-BA reserves the right to recheck the requirement of routine practice data collection and evaluations and to adapt or cancel the resolution on the requirement of routine practice data collection and evaluations. This may result in changes with regard to the preparation of the study protocol or the statistical analysis plan (SAP).

Taking into account the expected extension of the therapeutic indications, the following requirements arise:

1.1 Question according to PICO scheme

Population	▪ Pre-symptomatic patients with 5q-associated SMA and up to three SMN2 gene copies ▪ Symptomatic patients with clinically diagnosed SMA Type 1 ▪ Symptomatic patients with a clinically diagnosed SMA Type 2 and up to three SMN2 gene copies ▪ Symptomatic patients with a clinically diagnosed SMA Type 3 and up to three SMN2 gene copies
Intervention	▪ Risdiplam The marketing authorisation and the dosage information in the product information of the active ingredients must be taken into account.
Comparator	▪ Therapy according to doctor's instructions taking into account nusinersen and onasemnogene abeparvovec The marketing authorisation and the dosage information in the product information of the active ingredients must be taken into account.
Outcome	Mortality ▪ Deaths Morbidity ▪ Motor function (raised with age-appropriate tools) *and* ▪ Achievement of motor milestones ("Motor development milestones" of the WHO) *and* ▪ respiratory function (need for [permanent] ventilation) *and* ▪ bulbar function (ability to swallow and speak, need for non-oral nutritional support) *and* ▪ further complications of the disease (e.g. pain, orthopaedic complications) Side effects ▪ Serious adverse events (SAE) ▪ Adverse events leading to hospitalisation ▪ Serious specific adverse events: Retinal toxicity, effect on epithelial tissue, thrombocytopenia, renal toxicity, hydrocephalus, hepatotoxicity, cardiac events, inflammation of spinal ganglion cells

1.2 Type and methods of data collection

Taking into account the question of the routine practice data collection and the methodological limitations of non-randomised comparisons, the following requirements are placed on the study design and the data source for the present routine practice data collection.

1.2.1 Requirements for the study design

- Non-randomised comparison of risdiplam and data on nusinersen and onasemnogene abeparvovec collected in parallel as well as such data not collected in parallel within one data source, provided that the data not collected in parallel also meet the stated data quality requirements in section 1.2.2.

1.2.2 Data source requirement

- Use of indication registers as a data source that meet the requirements of routine practice data collection and fulfil at least the following quality criteria[1]:
  - Detailed registry description (protocol)
  - Exact definition or operationalisation of exposures (type and duration of medicinal therapy and other concomitant therapies), clinical events, endpoints and confounders
  - Use of standard classifications and terminologies
  - Use of validated standard data collection tools (questionnaire, scales, tests)
  - Training courses on data collection and recording
  - Implementation of a consus disease-specific core data set
  - Use of exact dates for the patient, the disease, important examinations and treatments/ interventions
  - Clearly defined inclusion and exclusion criteria for registry patients
  - Strategies to avoid selection bias in patient inclusion to achieve representativeness
  - Specifications to ensure completeness of data per data collection time point and completeness of data collection time points
  - Source data verification for 100% of patients per data collection site for the primary endpoint and for at least 10% of randomly selected patients per data collection site for all other endpoints over the period since the start of data collection
  - Ensuring scientific independence and transparency of the registry
- Use of an indication registry in which treatment of spinal muscular atrophy is carried out in accordance with the German daily care or is sufficiently similar to care in Germany

[1] IQWiG Rapid Report A21-131: Concept for routine practice data collection - risdiplam.

1.2.3 Primary registry and integration of further registries

- Use of the SMArtCARE registry as primary registry, provided that the quality criteria mentioned in section 1.2.2 are fulfilled
- It is also possible to integrate other registries, taking into account all the data source requirements mentioned in section 1.2.2

1.3 Duration and scope of data collection

- Observation of motor development under therapy: until month 36

As an approximation of the appropriate sample size for routine practice data collection, the following sample size is assumed as a result of an orienting sample size estimate, based on the combined endpoint of mortality/ permanent ventilation:

- approx. 125 patients (orienting sample size estimate)

1.4 Evaluations of the data for the purpose of the benefit assessment

The pharmaceutical company shall submit the following evaluations to the G-BA:

- Interim analyses

  Evaluations of 2 interim analyses shall be presented. The relevant times for the performance of the interim analyses shall be the times specified in section 2.3.
  The interim analyses shall be performed according to the specifications in the study protocol and statistical analysis plan (see section 1.5). In the process, a check for discontinuation due to futility must also be carried out for each interim analysis.

  On the 1st interim analysis 18 months after the date of the start of routine practice data collection, to be defined by means of a declaratory resolution:

  Based on this interim analysis, a final sample size estimate will be made using the more precise effect assumptions rendered possible. If necessary, this can also be carried out at this time on the basis of other benefit endpoints (such as motor development or a different operationalisation of mandatory ventilation) and taking into account a shifted hypothesis boundary in accordance with the procedure in IQWiG's concept[1]. Alternatively, if the pharmaceutical company does not seek an advantage in benefit endpoints (such as the aforementioned achievement of motor milestones), a sample size estimate based on another endpoint can be made. Here, too, shifted hypothesis boundaries must be applied in each case. The pharmaceutical company shall present in the interim analysis the basis on which it has made the final sample size estimate.

The interim analyses shall be prepared on the basis of module 4 of the dossier template, providing the full texts and study documents.

- Final evaluations for the purpose of the renewed benefit assessment

  The final evaluations shall be carried out according to the specifications in the study protocol and statistical analysis plan. For the transmission of the final evaluations to the G-BA, the time specified in section 3 applies.

The final evaluations shall be prepared in a dossier in accordance with the provisions of Section 9 paragraphs 1 to 7 of the Rules of Procedure of the G-BA.

1.5 Requirements for the preparation of the study protocol and statistical analysis plan

The pharmaceutical company shall prepare a study protocol and a statistical analysis plan before carrying out routine practice data collection. In this context, they shall in particular provide the following information in advance with regard to the evaluation of the data:

- Information on the statistical methods and models used, as well as naming the procedures and the criteria used in model selection and adaptation
- Information on the expected scope and reasons for missing data, as well as measures to avoid missing data and evaluation strategies to deal with missing data
- Information on dealing with implausible data and outliers
- Information on planned sensitivity analyses
- Information on the identification, as well as the adequate, pre-specified adjustment for confounders
- Information on the investigation of potential effect modifiers
- Information on subgroup analyses based on the number of SMN2 gene copies for pre-symptomatic patients with 5q-associated SMA and up to three SMN2 gene copies, in order to check whether a joint evaluation is appropriate
- Information to check the extent to which the data on nusinersen and onasemnogene abeparvovec collected in parallel, as well as data not collected in parallel, are suitable for pooled analysis
- Information to check the extent to which any data comparing risdiplam versus nusinersen and onasemnogene abeparvovec from different data sources are suitable for a pooled analysis
- Information on dealing with patients who change their medicinal therapy or receive combination therapy
- Information on interim analyses taking into account the requirements under section 1.4 and the specifications under section 2.3
- Information on discontinuation criteria due to futility

2. Requirements for checking whether the pharmaceutical company has fulfilled its obligation to carry out routine practice data collection and evaluations

2.1 Submission of a study protocol as well as the statistical analysis plan for coordination with the G-BA

The final drafts for a study protocol and for a statistical analysis plan prepared by the pharmaceutical company shall be submitted to the G-BA for approval no later than 4 weeks

after the positive opinion for the extension of the therapeutic indication of risdiplam for patients aged 0 to 2 months, but not earlier than 5 months after entry into force of the present resolution.

The G-BA, with the involvement of IQWiG, carries out a review of the study protocol and the statistical analysis plan and usually communicates the result to the pharmaceutical company in writing within 12 weeks.

Before submitting the requested documents to the G-BA, the pharmaceutical company has the option to request a consultation with the G-BA according to Section 35a, paragraph 7 SGB V in conjunction with Section 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV). The subject of such consultation is, in particular, the drafts for a study protocol as well as for a statistical analysis plan. In order to enable the pharmaceutical company to adequately consider the aspects addressed in the consultation when preparing the study protocol and statistical analysis plan, the request for consultation must be submitted to the G-BA by 19 August 2022 at the latest.

If the Federal Joint Committee determines during the first submission of the study protocol and statistical analysis plan that the requirements of routine practice data collection and evaluations are insufficiently implemented, the pharmaceutical company is given the opportunity to revise the study documents once. The Federal Joint Committee shall adopt a declaratory resolution in this regard in the procedure for routine practice data collection and evaluations, which shall set out the necessary need for adaptation of the study documents. The deadline for submission of the revised statistical analysis plan and study protocol is 4 weeks, unless otherwise specified in the declaratory resolution.

2.2 Submission of information on the course of data collection (in particular information on the status of recruitment)

6, 18 and 30 months after the date of commencement of the routine practice data collection to be defined by means of a declaratory resolution, the pharmaceutical company shall provide the G-BA in particular with information on:

- the number and the respective medicinal treatment of the patients included so far,
- patient-related observation periods, and
- any deviations regarding the expected number of recruits.

The G-BA may confirm the submitted statistical analysis plan and the study protocol by means of a declaratory resolution subject to the condition that further adaptations to the study documents deemed mandatory for the implementation of the requirements from this resolution must be made. In this case, the final study documents shall be submitted to the G-BA together with the submission of information on the course of data collection 6 months after the date of the start of routine practice data collection, which is to be defined by means of a declaratory resolution.

2.3 Submission of interim analyses

At the following times after the time of the start of routine practice data collection, which is to be defined by means of a declaratory resolution, interim analyses shall be carried out and corresponding evaluations shall be submitted to the G-BA, taking into account the requirements specified in section 1.4:

- 18 months after the start of routine practice data collection
- 30 months after the start of routine practice data collection

3. Deadline for the submission of evaluations of the data collected as part of the routine practice data collection

For the performance of a new benefit assessment, the evaluations of data collected as part of the routine practice data collection must be submitted by **1 August 2026** at the latest.

The submission of these evaluations must be made in the form of a dossier in accordance with the provisions of Chapter 5, Section 9, paragraphs 1 to 7 of the Rules of Procedure of the G-BA, taking into account the requirements of this resolution in accordance with Chapter 5, Section 58 of the Rules of Procedure of the G-BA.