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)
Onasemnogene abeparvovec (spinal muscular atrophy); requirement of routine practice data collection and evaluations – amendment

of 21 September 2023

Contents

1. Legal basis

According to Section 35a, paragraph 3b, sentence 1 SGB V, the Federal Joint Committee (G-BA) can demand the pharmaceutical company to submit routine practice data collections and evaluations for the purpose of the benefit assessment within a reasonable period of time for the following medicinal products:

1. in the case of medicinal products authorised to be placed on the market in accordance with the procedure laid down in Article 14, paragraph 8 of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1), as last amended by Regulation 162 Rules of Procedure last revised: 16 December 2020 (EU) 2019/5 (OJ L 4, 7.1.2019, p. 24), or for which a marketing authorisation has been granted in accordance with Article 14-a of Regulation (EC) No 726/2004; and
2. for medicinal products approved for the treatment of rare diseases under Regulation No. 141/2000.

2. Key points of the resolution

In its session on 4 February 2021, the G-BA decided on the requirement of routine practice data collection and evaluations for the active ingredient onasemnogene abeparvovec in accordance with Section 35a SGB V.

Subsequent to the publication of the resolution on the G-BA's website, there has been further development with regard to the generally recognised state of medical knowledge, taking into account the resolution on the benefit assessment of risdiplam of 21 October 2021. On 20 July 2023, risdiplam also received a positive opinion from the European Medicines Agency (EMA) for the extension of the therapeutic indication for patients aged 0 to 2 months. The marketing authorisation for the extension of the therapeutic indication for patients aged 0 to 2 months was granted on 16 August 2023.

This results in changes regarding the requirement of routine practice data collection and evaluations for onasemnogene abeparvovec (spinal muscular atrophy) by the G-BA.

On the changes in detail

The active ingredient risdiplam was approved on 26 March 2021 for the treatment of 5q spinal muscular atrophy (SMA) in patients 2 months of age and older, with a clinical diagnosis of type 1, type 2 or type 3 SMA or with one to four SMN2 gene copies.

By resolution of 21 October 2021, regarding the active ingredient risdiplam, the G-BA declared a hint for a non-quantifiable additional benefit of risdiplam compared to nusinersen for patients 2 months of age and older with type 1 5q SMA. A hint for a non-quantifiable additional benefit of risdiplam compared to "best supportive care" was found for patients 2 months of age and older with type 3 5q SMA for whom intrathecal application of nusinersen is not an option. An additional benefit compared to the appropriate comparator therapy is not proven

for all other patient groups. The additional benefit for patients 2 months of age and older with type 1 5q SMA is based on a "naive" comparison of individual arms from different studies, in which, however, it cannot be ruled out with certainty that the significant differences to the advantage of risdiplam are solely due to a systematic bias caused by confounding variables. However, based on the differences observed, it can be assumed that risdiplam is at least not inferior to nusinersen. In addition, oral administration of risdiplam is assumed to have a noticeable advantage over intrathecal administration of nusinersen, especially in younger children. In summary, the available evidence for the active ingredient risdiplam, although limited, indicates that risdiplam is not inferior to nusinersen for the largest patient group in terms of SMA types (patients with type 1 5q SMA).

Since only data from symptomatic SMA patients without a direct comparison to existing alternative therapies were available with the marketing authorisation of the active ingredient risdiplam, the G-BA also decided on 21 July 2022 on the requirement of routine practice data collection and evaluations according to Section 35a SGB V for this active ingredient.

In the written submission procedure for the active ingredient risdiplam, the AkdÄ points out that the prescription of the active ingredients approved for SMA in everyday care is also based on the authorisation status of the medicinal products due to a lack of comparator study data. The clinical scientific-medical societies and representatives of the SMArtCARE registry also argued that, according to current data basis, about 90-95% of all children affected with SMA are detected in newborn screening and are treated immediately in the case of the presence of ≤3 SMN2 gene copies. Therefore, especially for the group of pre-symptomatic patients with 5q SMA with up to 3 copies of the SMN2 gene, it can be assumed that without extending the marketing authorisation of risdiplam to the first two months of life, there will not be sufficient patients treated with risdiplam.

The active ingredient risdiplam received a positive opinion from the European Medicines Agency (EMA) on 20 July 2023 for the extension of the existing indication to patients with SMA aged 0 to 2 months. The marketing authorisation for the extension of the therapeutic indication for patients aged 0 to 2 months was granted on 16 August 2023.

Taking into account the above aspects and the extension of the marketing authorisation for risdiplam, the G-BA considers risdiplam to be a relevant comparator for the requirement of routine practice data collection for onasemnogene abeparvovec, which is why the amendment of the Pharmaceuticals Directive on which the present resolution is based is considered appropriate and necessary. Based on the current evidence and taking into account the current German health care context, the G-BA determines for pre-symptomatic patients with 5q SMA and up to 3 copies of the SMN2 gene, as well as for symptomatic patients with 5q SMA and a clinically diagnosed SMA type 1 and symptomatic patients with 5q SMA and a clinically diagnosed SMA type 2 and up to 3 copies of the SMN 2 gene, a therapy according to doctor's instructions, taking into account nusinersen and risdiplam as comparators for the required routine practice data collection for onasemnogene beparvovec.

The following criteria were used in the assessment:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.

2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

For the treatment of 5q spinal muscular atrophy, the active ingredients nusinersen and risdiplam are approved in addition to the active ingredient onasemnogene abeparvovec.

In the above-mentioned therapeutic indication, there is a G-BA resolution on the benefit assessment of nusinersen and a resolution for risdiplam for patients 2 months of age and older in accordance with Section 35a SGB V. By letter dated 27 July 2021, the pharmaceutical company of the active ingredient risdiplam was requested to submit a dossier regarding patients aged 0-2 months.

For the present requirement of routine practice data collection and evaluations, a therapy according to doctor's instructions, taking into account nusinersen and risdiplam, is defined as a comparator for the routine practice study. The G-BA determines risdiplam as part of the comparator "therapy according to doctor's instructions" for the routine practice study, taking into account the required duration of the routine practice data collection, during which a new situation may arise with regard to the generally accepted state of medical knowledge in the therapeutic indication in question. In principle, this is to be considered separately from the determination of the appropriate comparator therapy, which only becomes legally binding with the resolution on the benefit assessment according to Section 35a, paragraph 3 SGB V.

In accordance with the aforementioned explanations, data from patients treated with nusinersen and data from patients treated with risdiplam are to be collected in the comparator arm for the presently required patient population of the routine practice data collection according to Section 35a, paragraph 3b, sentence 1 SGB V.

This change is to be implemented within the framework of an addendum to the study protocol and the statistical analysis plan for the RPDC study for the active ingredient onasemnogene abeparvovec in accordance with the VerfO requirements and to be submitted together with the 1st interim analysis for review. The final sample size estimate to be made by the pharmaceutical company based on the 1st interim analysis should already take the change in the comparator into account.

The adjustments to the study protocol and the SAP required on the basis of the present change in the comparator are to be submitted to the G-BA by 4 February 2024.

An evaluation of the data collected on the basis of the adapted study protocol and SAP for the modified comparator "therapy according to doctor's instructions taking into account nusinersen and risdiplam" is to be submitted to the G-BA (for the first time) in the course of the 2nd interim analysis.

3. Submission according to Section 35a, paragraph 3b, sentences 7 and 8 SGB V

The amendment resolution and the justification were sent to the participants in accordance with Section 35a, paragraph 3b, sentences 7 and 8 SGB V for written submission. The deadline for making the written submissions was 23 August 2023.

4. 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.

5. Process sequence

Subsequent to the adoption of resolution of 4 February 2021 on an amendment to the Pharmaceuticals Directive (AM-RL) Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V – onasemnogene abeparvovec, a further development with regard to the generally recognised state of medical knowledge has resulted, taking into account the resolution on the benefit assessment of risdiplam of 21 October 2021. On 20 July 2023, risdiplam also received a positive opinion from the European Medicines Agency (EMA) for the extension of the therapeutic indication for patients aged 0 to 2 months.

This results in changes to the requirements of the G-BA with regard to the routine practice data collection and evaluations.

The issue was discussed in the working group WG RPDC and in the Subcommittee on Medicinal Products.

At its session on 8 August 2023, the subcommittee unanimously decided on the written submission of participants in accordance with Section 35a, paragraph 3b, sentences 7 and 8 SGB V.

The evaluation of the written submissions received was discussed at the session of the subcommittee on 12 September 2023, and the proposed resolution was approved.

At its session on 21 September 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
WG RPDC	17 April 2023 15 May 2023 18 July 2023 3 August 2023	Consultation on an amendment of the Pharmaceuticals Directive: Requirement of an RPDC and evaluations *(change of the comparator)*

Subcommittee Medicinal products	8 August 2023	Discussion and consensus on the draft resolution on the amendment of the requirement for an RPDC and evaluations *(amendment of the comparator)* Initiation of the submission procedure
WG RPDC	7 September 2023	Evaluation of the written submission Preparation of a draft resolution for the amendment of the requirement for an RPDC and evaluations *(amendment of the comparator)*
Subcommittee on Medicinal Products	12 September 2023	Concluding discussion of the draft resolution
Plenum	21 September 2023	Resolution on an amendment of the Pharmaceuticals Directive: Requirement of an RPDC and evaluations *(change of the comparator)*

Berlin, 21 September 2023

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

Prof. Hecken