Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on the Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII - Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Valoctocogen roxaparvovec (severe haemophilia A); requirement of routine data collection and evaluations

of 2 February 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 authorised for the treatment of rare diseases under Regulation No. 141/2000.

2. Key points of the resolution

The active ingredient valoctocogen roxaparvovec received a conditional marketing authorisation (Article 14-a of Regulation (EC) No 726/2004, as last amended by Regulation (EU) 2019/5) for the treatment of severe haemophilia A from the European Commission (EC) on 24 August 2022. The first listing in the directory services in accordance with Section 131, paragraph 4 SGB V, took place on 15 September 2022. In addition, the active ingredient valoctocogen roxaparvovec was approved as a medicinal product for the treatment of rare diseases (orphan drug) under Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999.

On the basis of the ongoing or completed studies on valoctocogen roxaparvovec considered for the marketing authorisation, the G-BA identified gaps in the evidence, particularly for the following aspects relevant to the early benefit assessment, which justify the necessity of a routine practice data collection and evaluations according to Section 35a, paragraph 3b, sentence 1 SGBV for the active ingredient valoctocogen roxaparvovec:

- Data to assess the long-term (additional) benefits and harms of treatment with valoctocogen roxaparvovec for adult patients with severe haemophilia A (congenital factor VIII deficiency) without a history of factor VIII inhibitors;
- Comparative data of treatment with valoctocogen roxaparvovec versus existing treatment alternatives for adult patients with severe haemophilia A (congenital factor VIII deficiency) without a history of factor VIII inhibitors.

Currently, only data without a direct comparison to existing treatment alternatives are available for the active ingredient valoctocogen roxaparvovec. Taking into account the aforementioned evidence gaps, the question of the present routine practice data collection comprises the assessment of the benefit and harm profile of valoctocogen roxaparvovec in comparison with existing therapy alternatives and the evaluation of the sustainability of the therapy success for adult patients with severe haemophilia A without a history of factor VIII inhibitors.

By resolution of 3 February 2022, the G-BA initiates a procedure for the requirement of a routine practice data collection according to Section 35a, paragraph 3b, sentence 1 SGB V for the active ingredient valoctocogen roxaparvovec.

A concept was drawn up in preparation for the resolution on the requirement of routine data collection and evaluations. The concept contains in particular requirements for:

1. the type, duration and scope of data collection,
2. the research question (PICO framework: patient/population, intervention, comparison, outcomes) that is to be the subject of the data collection and evaluations, including the patient-relevant endpoints to be recorded,
3. the data collection methods,
4. the evaluations by the pharmaceutical company according to Section 50, paragraphs 2 and 3 of the VerfO.

The G-BA decides whether to prepare the concept itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG) to do so. In the present case, the G-BA commissioned IQWiG to prepare the concept. The expert bodies according to Section 35a, paragraph 3b, sentences 7 and 8 SGB V made a written submission in drawing up the concept. The submission took place in such a way that the expert bodies were given the opportunity in writing to comment on the requirements of routine practice data collection and evaluations in accordance with the concept that had been drawn up. In addition, expert consultation was held.

In preparing the concept, ongoing and planned data collections were taken into account, especially those resulting from conditions or other ancillary provisions imposed by the marketing authorisation or licensing authorities. A review of the ongoing or planned interventional studies on valoctocogen roxaparvovec commissioned by the marketing authorisation authority has shown that no comparative data are likely to be collected as part of the obligation to carry out post-authorisation measures, as the demands listed relate exclusively to the active ingredient valoctocogen roxaparvovec.

Based on this, the G-BA classifies the studies commissioned by the marketing authorisation authority as not suitable for improving the existing evidence base sufficiently and for the purpose of the benefit assessment.

Based on the above-mentioned question, the G-BA, on the basis of IQWiG's concept and the submission of the expert bodies in drawing up the concept, decided by the present resolution on the requirements of routine practice data collection and evaluations, as well as on the specifications for the review of the obligation to perform and on the deadline for the submission of evaluations.

2.1 Requirements for routine practice data collection and evaluations

2.1.1 Question according to PICO scheme

Patient population

According to the marketing authorisation, the target population for the active ingredient valoctocogen roxaparvovec includes adult patients with severe haemophilia A (congenital factor VIII deficiency) without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5). For the present requirement of routine data collection and evaluations according to Section 35a paragraph 3b sentence 1 SGB V, the pharmaceutical company shall collect and evaluate comparator data for the patient population of adult patients with severe haemophilia A (congenital factor VIII deficiency) without a history of factor VIII inhibitors.

The AAV5 antibody status is a relevant criterion in the treatment decision for or against gene therapy with valoctocogen roxaparvovec, but is currently not regularly collected in patients with haemophilia A. In the submission procedure, it was pointed out that the AAV5 antibody status has no connection with the severity grade of haemophilia and therefore does not influence the course of the disease. Therefore, in the present requirement of routine data collection and evaluations, the global patient population is not restricted to the lack of detectability of AAV5 antibodies.

Patients with positive AAV5 antibody status cannot be treated with valoctocogen roxaparvovec and continue to receive the factor VIII preparations or emicizumab. Despite the positive AAV5 antibody status, the comparability of this patient group with the patient population that has a negative AAV5 antibody status and can be treated with valoctocogen roxaparvovec is considered to be sufficiently high, as only the positive AAV5 antibody status prevents therapy with valoctocogen roxaparvovec.

Nevertheless, the G-BA recommends that tests performed with regard to the AAV5 antibody status be recorded in the routine practice data collection. For these patients, AAV5 antibody testing can be defined as a uniform start of observation. In addition, for patients who are not eligible for therapy with valoctocogen roxaparvovec solely because of positive AAV5 antibody status, a high degree of comparability to the patient population treated with valoctocogen roxaparvovec can be assumed. Therefore, from the G-BA's point of view, sensitivity analyses on the patient population with known AAV5 antibody status appear reasonable.

Intervention

In accordance with the present requirement of routine data collection and evaluations according to Section 35a, paragraph 3b, sentence 1 SGB V, the intervention includes the active ingredient valoctocogen roxaparvovec. The marketing authorisation and the dosage information in the product information of valoctocogen roxaparvovec (Roctavian) must be taken into account. According to the product information, valoctocogen roxaparvovec should only be administered to patients in whom the absence of anti-AAV5 antibodies has been demonstrated using a validated assay.

Comparator therapy

The following criteria were applied:

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.

on 1. Medicinal products with the following active ingredients are currently approved for the treatment of haemophilia A:

- Recombinant factor VIII products contain the genetically engineered human factor VIII glycoprotein. The factor VIII glycoproteins differ, among other things, in the length of their side chains.
  - Octocog alfa contains the natural human factor VIII glycoprotein with the complete amino acid sequence[1]. Rurioctocog alfa pegol and Damoctocog alfa pegol are both pegylated, recombinant blood coagulation factor-VIII Octocog alfa.
  - Moroctocog alfa has a truncated side chain compared to the natural factor VIII glycoprotein.
  - Turoctocog alfa has a truncated side chain compared to the natural factor VIII glycoprotein.
  - Simoctocog alfa is composed of the active domains (domains A and C) of human factor VIII, domains A2 and A3 are linked by a linker sequence[1].
  - Efmoroctocog alfa has a truncated side chain compared to the natural factor VIII glycoprotein, covalently bound to the Fc domain of human immunoglobulin G1.

[1] Various proprietary medicinal products are available.

– Lonoctocog alfa is a single-chain polypeptide with a truncated B-domain that allows for a covalent bridge to link the factor VIII heavy and light chains.

All preparations are approved for the treatment and prophylaxis of haemophilia A. The pegylated factor VIII preparations rurioctocog alfa pegol and damoctocog alfa pegol are only approved for patients with haemophilia A aged 12 years or older.

- Human plasma factor VIII preparations[1] contain the human-identical factor VIII glycoprotein obtained from cryoprecipitates: They are obtained from large human plasma pools and are approved for the treatment and prevention of haemophilia A.
- A human plasma fraction enriched with factor VIII inhibitor bypassing activity is approved for the treatment and prevention of bleeding in haemophilia A patients with factor VIII inhibitor.
- A recombinant blood coagulation factor VIIa preparation (active ingredient: Eptacog alfa) is approved for the treatment of bleeding and prevention of bleeding associated with surgical or invasive procedures in, among others, patients with congenital haemophilia with inhibitors of coagulation factor VIII. It is not approved for the permanent treatment of moderate to severe haemophilia A requiring replacement.
- Emicizumab is a bispecific antibody that combines activated factors IX and factor X to replace the function of the missing activated factor VIII. Emicizumab is approved for the routine prophylaxis of patients with haemophilia A and existing factor VIII inhibitors on the one hand and for the routine prophylaxis of bleeding in severe haemophilia A without existing factor VIII inhibitors on the other hand.

on 2. A non-medicinal treatment cannot be considered an comparator therapy in the therapeutic indication.

on 3. For the treatment of haemophilia patients, the guideline Outpatient Treatment in Hospitals according to Section 116b SGB V (Annex 2, No. 2: Diagnosis and care of patients with coagulation disorders (haemophilia)). In the therapeutic indication "haemophilia A", the following resolutions from the G-BA on the benefit assessment of medicinal products according to Section 35a SGB V are available:

- Turoctocog alfa (resolution of 3 July 2014)
- Simoctocog alfa (resolution of 7 May 2015)
- Efmoroctocog alfa (resolution of 16 June 2016)
- Lonoctocog alfa (resolution of 20 July 2017)
- Emicizumab (resolutions of 20 September 2018 and 5 September 2019)
- Rurioctocog alfa pegol (resolution of 1 November 2018)
- Damoctocog alfa pegol (resolution of 20 June 2019)
- Turoctocog alfa pegol (resolution of 6 February 2020)

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 therapeutic indication. 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 Comparator Therapy").

In the overall view of the aggregated evidence, the recombinant and human plasma-derived factor VIII preparations are to be regarded as equivalent and are therefore equally eligible as comparator therapy. No evidence-based data have been found on therapeutic efficacy, side-effect profile (e.g. development of inhibitory haemophilia) or safety risk (e.g. risk of infection) that would lead to recombinant or human plasma-derived factor VIII preparations being regularly preferred in the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). This also applies to recombinant factor VIII preparations with prolonged half-life, which are equally covered by the comparator therapy.

A human plasma fraction enriched with factor VIII inhibitor bypassing activity is only approved for patients with existing factor VIII inhibitors and is therefore not considered as a comparator therapy for the present therapeutic indication.

With emicizumab, another medicinal product is approved in the present therapeutic indication. Since March 2019, in addition to the routine prophylaxis of bleeding in patients with existing factor VIII inhibitors, the marketing authorisation also covers the routine prophylaxis of bleeding in severe haemophilia A without existing factor VIII inhibitors.

On the part of the scientific-medical societies, emicizumab was mentioned as another relevant therapy option for the prophylactic treatment of patients with severe haemophilia A (factor VIII < 1 %) without factor VIII inhibitors within the framework of the present procedure for the requirement of a routine practice data collection and evaluations.

In the overall view of the currently available evidence, however, no unanimous therapy recommendation can be derived for the use of emicizumab in the present therapeutic indication. Within the framework of the benefit assessment according to Section 35a SGB V, it was determined that the additional benefit of emicizumab compared to plasmatic or recombinant blood coagulation factor VIII preparations in patients with severe haemophilia A (hereditary factor VIII deficiency, FVIII < 1 %) without factor VIII inhibitors who are eligible for routine prophylaxis is not proven.

For the present requirement of routine data collection and evaluations, emicizumab is defined as a comparator for the routine practice study in addition to the recombinant and human plasma-derived factor VIII preparations. The G-BA determines emicizumab as a comparator 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.

Taking into account the aspects described, in the overall view, the G-BA defines a therapy according to doctor's instructions as a comparator for the present routine practice data collection, taking into account recombinant or human plasma-derived blood coagulation factor VIII preparations and emicizumab. In accordance with the aforementioned explanations, data on treatment with recombinant or human plasma-derived coagulation factor VIII preparations and emicizumab are to be collected for the routine practice data collection according to Section 35a paragraph 3b sentence 1 SGB V for the patient population required in this case.

It is assumed that the patient population in the present indication is haemophilia patients requiring factor VIII replacement. Patients in the therapeutic indication of valoctocogen roxaparvovec are assumed to be eligible for prophylaxis (not for treatment on demand). A treatment on demand alone is not considered an adequate comparator therapy.

Outcome

Comparator data on the following endpoint categories shall be collected for the patient population required here for routine practice data collection in accordance with Section 35a, paragraph 3b, sentence 1 SGB V: Mortality, morbidity, health-related quality of life and side effects.

In the present therapeutic indication, the reduction of bleeding events or the achievement of a bleeding-free state is of particular relevance for the patients. Against this background, the patient-reported assessment of bleeding, especially severe and life-threatening bleeding as well as joint bleeding, in the registry study is of high importance for the comparison of valoctocogen roxaparvovec versus coagulation factor VIII preparations and emicizumab. In addition, patient-reported endpoints on pain, joint function and health-related quality of life are to be collected with validated instruments at uniform data collection time point.

If no indication-specific measurement instrument can be identified to assess health-related quality of life or symptomatology, generic instruments can also be used. The selection of appropriate instruments to collect patient-reported endpoints on symptomatology and health-related quality of life in the valoctocogen roxaparvovec routine practice data collection should be outlined during the development of the study protocol (SP) and statistical analysis plan (SAP).

With regard to the implementation of the assessment of health-related quality of life, the pharmaceutical company has to explain whether an adaptation of the identified indication register to this requirement is possible and within which period of time this can be realised.

The G-BA reserves the right to review whether, after submission of the study protocol and the statistical analysis plan, the requirement to assess health-related quality of life is waived within the framework of a weighing decision in the specific case at hand, insofar as the adaptation of the identified indication registry to this requirement would be disproportionate.

In addition to the recording of symptomatology and health-related quality of life, the recording of overall survival is also considered necessary, as the individual symptomatology of the subjects can have an influence on life expectancy.

With regard to side effects, the overall rates of serious adverse events (SAE) should be mapped via events leading to hospitalisation or death.

In addition, defined specific adverse events should be recorded, if indicated, with indication of the respective severity. Relevant specific adverse events in the present therapeutic indication may include, for example, the formation of factor VIII inhibitors, thromboembolic events, symptomatic liver damage and malignant neoplasms. The specific AEs should address valoctocogen roxaparvovec as well as the recombinant and plasmatic factor VIII preparations and emicizumab, and ideally should be coded using the MedDRA system.

In its written contribution, the registry operator explains that an assessment of adverse events (AEs) in the DHR is redundant to the already existing, legally obligatory reporting to the Paul Ehrlich Institute. In the expert consultation, the scientific-medical societies explained that due to the novelty of gene therapy, an assessment of side effects should be carried out as part of the routine practice data collection. Overall, the G-BA considers the structured and mandatory collection of serious AEs to be required for the necessary weighing of the benefits and harms of valoctocogen roxaparvovec versus the comparator therapy. In addition, the collection of specific adverse events is considered necessary in the context of the routine practice data collection; these are not covered by the legally obligatory reporting of AEs to the Paul Ehrlich Institute.

In addition, supplementary information on the number of factor concentrates and emicizumab consumed, separately for on-demand and prophylactic treatment, as well as the time of resumption of prophylactic therapy will be recorded. This information is relevant for assessing the course of the disease during therapy with valoctocogen roxaparvovec.

2.1.2 Type and methods of data collection

According to Section 35a, para. 3b SGB V, the Federal Joint Committee can demand indication-related data collection without randomisation for routine practice data collection.

For the present requirement of routine practice data collection, indication registries that meet the requirements for routine practice data collection and at least fulfil the quality criteria specified in the resolution shall be used as the data source. The minimum data quality requirements mentioned are based on the national and international quality criteria for registries mentioned in the IQWiG concept, whereby the focus was placed on the quality

criteria for standardisation and validity of data collection, as well as for sample collection, which were considered particularly relevant for the present requirement.

In order to ensure the suitability of the data collected, the use of an indication registry is also required in which treatment of severe haemophilia A is carried out in accordance with German daily care or is sufficiently similar to care in Germany.

The guarantee of sufficiently similar care in Germany, which is required when using (indication) registries, should make it possible to integrate data from other European countries without compromising data quality. If there are relevant differences in the standard of care in another country, registry data from this country should not be used for the present routine practice data collection and evaluations.

Based on the available information, the German Haemophilia Registry (DHR) may be suitable as a primary data source for a routine practice data collection, provided that the still existing limitations are eliminated. The adaptations required for the routine practice data collection refer in particular to the following aspects in accordance with the IQWiG concept[2]:

- Increase in the number of patients in individual notification
- Introduction of mandatory data fields to be documented on inclusion and exclusion criteria as well as relevant endpoints
- Assessment of adverse events
- Assessment of patient-reported endpoints on symptomatology and health-related quality of life
- Uniform assessment and reporting dates
- Systematic identification of relevant confounders and expansion of the data set to include previously unrecorded, relevant confounders
- Supplementing the measures to ensure the accuracy of the data (introduction of source data verification based on a sample of, e.g. 5% or 10% of the data records)

Provided that the quality criteria and requirements of routine practice data collection specified in this resolution can be implemented in the DHR, the DHR is to be used as the primary registry.

2.1.3 Duration and scope of data collection

The duration and scope of routine practice data collection result from the estimated suitable patient-related duration of observation and the estimated required number of patients (sample size).

[2] IQWiG Rapid Report A22-20 - Concept for routine practice data collection - valoctocogen roxaparvovec

The aim of the routine practice data collection is to determine the long-term benefits and harms of treatment with valoctocogen roxaparvovec compared to the comparator therapy. With the gene therapy valoctocogen roxaparvovec, a functional copy of the gene for the missing coagulation factor VIII is transfected into the liver cells in order to substitute the genetically caused deficiency of coagulation factor VIII. Preliminary observations indicate that factor VIII activity weakens after one to two years of gene therapy with valoctocogen roxaparvovec. For the routine practice data collection, the duration of observation should be at least three years from the end of recruitment.

As an approximation of the appropriate case number for the routine practice data collection, an orientational sample size estimate was performed based on the endpoints annual bleeding rate (ABR) and bleeding-free state.

Two scenarios were calculated for the endpoint bleeding-free. This results in case numbers of 1,554 and 516 patients, respectively, assuming a 1:5 distribution between intervention and comparator group and a responder rate of 35% under the comparator therapy. With a responder rate of 87.5% of patients receiving therapy with the intervention, the sample size is 516 patients; with a responder rate of 80.5% of patients receiving therapy with the intervention, the number of cases is 1,554 patients.

For the scenario based on the endpoint ABR, a 1:5 distribution was also assumed. Assuming an ABR of 0.85 under the intervention and an ABR of 3 under the comparator therapy, this results in a sample size of 397 patients. The ABR scenario was calculated using a negative binomial model and assuming a dispersion of 1.5.

In the submission procedure, it was pointed out that the willingness of patients for a therapy with valoctocogen roxaparvovec is estimated to be low due to the novelty of the gene therapy as well as highly effective therapy alternatives. Consequently, a 1:5 distribution between intervention and comparator group was assumed in the orienting sample size estimate.

The exemplary sample sizes presented are of a magnitude where it can be assumed that routine practice data collection is feasible in principle for the question at hand. The final sample size planning is part of the preparation of the statistical analysis plan and the study protocol by the pharmaceutical company.

When planning the number of cases for the present routine practice data collection, it must be ensured that a sufficient number of patients receiving treatment with recombinant or human plasma-derived coagulation factor VIII preparations is recruited to achieve adequate study power. In this regard, reference is made to the explanations under 2.2.1 on the determination of emicizumab as a comparator for the present requirement of routine data collection and evaluations.

2.1.4 Evaluations of the data collection for the purpose of the benefit assessment

The general requirements for the evaluation of comparator studies without randomisation must correspond to the planning of the evaluation of comparator studies with randomisation.

The information given in the resolution must be taken into account when drawing up the study protocol and statistical analysis plan prior to carrying out the routine practice data collection (see also section 2.1.5).

The evaluation of data from different data sources, i.e. different registries, should be done separately for each data source. Additional pooled analysis is possible after checking the suitability of data from different data sources. Information on the verification of suitability for pooled analysis should be set out accordingly in advance in the statistical analysis plan.

The pharmaceutical company shall perform the evaluations mentioned in the resolution (interim analyses and final evaluation) according to the specifications in the study protocol and the statistical analysis plan. The interim analyses shall be prepared on the basis of Module 4 of the dossier template with provision of the full texts and study documents, the final evaluations shall be prepared in a dossier in accordance with the provisions in Section 9, paragraphs 1 to 7 of the Rules of Procedure of the G-BA. The relevant times for conducting the interim analyses are the times specified in the resolution under section 2.3 and for submitting the final evaluations to the G-BA the time specified in the resolution under section 3.

The orienting sample size estimate is subject to uncertainties due to the small information base available and therefore represents a first hint of the required size of the study population. Against this background, the G-BA considers it expedient that a review is carried out by the pharmaceutical company during the course of the study, which may lead to an adjustment of the sample size. If necessary, this can also be carried out at this time on the basis of benefit endpoints other than those mentioned in the present resolution and taking into account a shifted hypothesis boundary in accordance with the procedure in IQWiG's[2] concept.

2.1.5 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 and evaluations. In this respect, the requirements for the information to be presented as described in the resolution shall be taken into account.

2.2 Specifications for reviewing whether the pharmaceutical company has fulfilled its obligation to carry out routine practice data collection and evaluations

The pharmaceutical company shall prepare a study protocol and a statistical analysis plan for approval by the Federal Joint Committee before carrying out the routine practice data collection and evaluations. Taking into account the time frame required for drafting, the pharmaceutical company shall submit the final drafts of a study protocol and a statistical analysis plan to the G-BA for approval by 2 July 2023.

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.

In order to be able to clarify queries during the preparation of the final drafts for a study protocol as well as for a statistical analysis plan, the pharmaceutical company has the possibility - before submitting the requested documents to the G-BA - to request 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). 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 3 March 2023 at the latest.

According to Section 35a para. 3b, sentence 10 SGB V, the data obtained and the obligation to collect data must be reviewed by the G-BA at regular intervals, but at least every 18 months.

With regard to the information on the course of data collection (in particular information on the status of recruitment), the pharmaceutical company shall provide the G-BA with information on the number and the respective medicinal treatment of the patients included to date, on patient-related observation periods and on possible deviations with regard to the expected number of recruits at intervals of 18 months.

The subject of the continuous review of the data obtained is in particular whether the data collection is carried out or not, or can no longer be carried out.

The pharmaceutical company shall submit three interim analyses to the G-BA 18, 36 and 54 months after the date of commencement of the routine practice data collection to be defined by means of a declaratory resolution. Within the framework of the first interim analysis, a review of the sample size estimate on the part of the pharmaceutical company is also to be carried out.

2.3 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 must be submitted by 1 February 2029 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.

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

In order to prepare a recommendation for a resolution on the initiation of a procedure for the requirement of a routine practice data collection (amendment of Annex XII of AM-RL) according to Section 35a, paragraph 3b SGB V, the Subcommittee on Medicinal Products commissioned a working group (WG routine practice data collection (RPDC)) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and the representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions. In addition, the competent higher federal authority, the Paul Ehrlich Institute, was involved in the consultation to assess the requirement of routine practice data collection according to Section 35a, paragraph 3b, sentence 1 SGB V.

The recommended resolution on the initiation of a procedure for the requirement of a routine practice data collection was discussed on 25 January 2022 at the subcommittee session and the draft resolution was approved.

At its session on 3 February 2022, the plenum resolved to initiate a procedure for the requirement of a routine practice data collection.

In conjunction with the resolution of 3 February 2022 regarding the initiation of a procedure for the requirement of a routine practice data collection, the G-BA commissioned IQWiG to scientifically develop a concept for routine practice data collection and evaluations for the purpose of preparing a resolution.

IQWiG's concept was submitted to the G-BA on 30 September 2022. On 4 October 2022, the written submission of the expert bodies according to Section 35a, paragraph 3b, sentences 7 and 8 SGB V was initiated. The deadline for making the written submission was 1 November 2022.

The expert consultation within the framework of the submission by the expert bodies took place on 21 November 2022.

The evaluation of the written submissions received and of the expert consultation was discussed at the session of the Subcommittee on 24 January 2023, and the proposed resolution was approved.

At its session on 2 February 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
WG RPDC	14 October 2021 11 November 2021 13 December 2021 13 January 2022	Consultation on the initiation of a procedure for the requirement of a routine practice data collection (amendment of Annex XII of the AM-RL), involvement of the higher federal authority
Subcommittee on Medicinal Products	25 January 2022	Concluding discussion of the draft resolution
Plenum	3 February 2022	Resolution on the initiation of a procedure for the requirement of a routine practice data collection (amendment of Annex XII of the AM-RL)
WG RPDC	14 November 2022	Information on written submissions received, preparation of the expert consultation
Subcommittee on Medicinal Products	21 November 2022	Implementation of the expert consultation
WG RPDC	1 December 2022 12 December 2022 5 January 2023 16 January 2023	Consultation on IQWiG's concept and on the specifications for the review of the obligation to conduct and submit evaluations, evaluation of the submission procedure
Subcommittee on Medicinal Products	24 January 2023	Concluding discussion of the draft resolution
Plenum	2 February 2023	Resolution on the requirement of routine practice data collection (amendment of Annex XII of the AM-RL)

Berlin, 2 February 2023

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

Prof. Hecken