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 Autologous Anti-CD19-transduced CD3+ Cells (relapsed or refractory mantle cell lymphoma); Requirement of Routine Practice Data Collection and Evaluations

of 21 July 2022

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 autologous anti-CD-19-transduced CD3+ cells received conditional marketing authorisation (Article 14-a of Regulation (EC) No. 726/2004) for the treatment of relapsed or refractory mantle cell lymphoma (MCL) from the European Commission (EC) on 14 December 2020. The first listing in the directory services in accordance with Section 131, paragraph 4 SGB V, took place on 15.03.2021.

On the basis of the ongoing or completed studies on autologous anti-CD19-transduced CD3+ cells that were taken into account for the marketing authorisation, the G-BA identified gaps in the evidence, particularly for the aspects mentioned below and relevant for the early benefit assessment, which justify the requirement of routine practice data collection and evaluations according to Section 35a, paragraph 3b, sentence 1 SGBV for the active ingredient autologous anti-CD19-transduced CD3+ cells:

- Data to assess the long-term (incremental) benefits and harms of treatment with autologous anti-CD19-transduced CD3+ cells for the approved patient population;
- Comparator data of treatment with autologous anti-CD19-transduced CD3+ cells vs existing therapeutic alternatives for the approved patient population

Currently, only data without comparison against existing therapeutic alternatives are available for the active ingredient autologous anti-CD19-transduced CD3+ cells with a median follow-up duration of about two years. The indirect comparisons presented within the framework of the benefit assessment according to Section 35a SGB V were not suitable for deriving statements on the extent of the additional benefit. Taking into account the gaps in the evidence mentioned above, the question of the present routine practice data collection

comprises the assessment of the benefit and harm profile of autologous anti-CD19-transduced CD3+ cells in comparison with existing therapeutic alternatives as well as the evaluation of the sustainability of the therapy success for patients with relapsed or refractory mantle cell lymphoma for whom treatment with autologous anti-CD19-transduced CD3+ cells is indicated.

By resolution of 7 October 2021, 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 autologous anti-CD-19-transduced CD3+ cells.

A concept was drawn up in preparation for the resolution on the requirement of routine practice 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 and non-interventional studies on autologous anti-CD19-transduced CD3+ cells 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 autologous anti-CD19-transduced CD3+ cells. 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 populations

According to the marketing authorisation, the target population for the active ingredient autologous anti-CD19-transduced CD3+ cells (hereinafter referred to as brexucabtagene autoleucel) comprises adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more systemic therapies that include a Bruton's tyrosine kinase (BTK) inhibitor. For the present requirement of routine practice 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 defined according to the marketing authorisation.

In a comparator study without randomisation, the comparability of the study populations or the fulfilment of positivity for the treatment options to be compared must be given. Due to the specific conditions of the patients, which must be given for a therapy with brexucabtagene autoleucel, the criteria for the suitability for a therapy with brexucabtagene autoleucel should be applied in the definition of the inclusion and exclusion criteria of the routine practice data collection and evaluations.

Intervention

In accordance with the present requirement of routine practice data collection and evaluations according to Section 35a, paragraph 3b, sentence 1 SGB V, the intervention includes the active ingredient brexucabtagene autoleucel. The marketing authorisation and the dosage information in the product information for brexucabtagene autoleucel (Tecartus®) must be taken into account.

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. In addition to brexucabtagene autoleucel, the active ingredients ibrutinib, lenalidomide and temsirolimus are explicitly approved for the treatment of relapsed

or refractory mantle cell lymphoma. Mantle cell lymphoma is a type of non-Hodgkin lymphoma. Bendamustine, carmustine, chlorambucil, cyclophosphamide, cytarabine, doxorubicin, trofosfamide, pixantrone, dexamethasone, prednisone, prednisolone, vinblastine, vincristine, bleomycin, etoposide, ifosfamide, mitoxantrone and methotrexate are also approved for the treatment of B-cell non-Hodgkin lymphoma.

On 2. Non-medicinal treatment includes allogeneic stem cell transplant, autologous stem cell transplant and radiotherapy.

On 3. In the mentioned therapeutic indication, the following resolutions from the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V are available:

- Pixantron (resolution of 16 May 2013)
- Ibrutinib (resolution of 21 July 2016)
- Autologous anti-CD19-transduced CD3+ cells (resolution of 5 August 2021).

In addition, the following resolutions on Annex VI to Section K of the Pharmaceuticals Directive - Prescribability of approved medicinal products in non-approved therapeutic indications (so-called off-label use) are available:

- Use of fludarabine in low or intermediate malignant B-non-Hodgkin lymphoma (B-NHL) other than chronic lymphocytic leukaemia (CLL) as specified in the marketing authorisation
- Rituximab in mantle cell lymphoma

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 Appropriate Comparator Therapy"). A written statement from the German Society for Haematology and Medical Oncology (DGHO) as well as the AkdÄ was available.

The evidence in the present therapeutic indication is extremely limited. In addition to the guideline of the British Society for Haematology (BSH), the guideline of the National Comprehensive Cancer Network (NCCN) is also available. From the present guidelines, it appears that there is no uniform treatment standard for the treatment setting of relapsed or refractory mantle cell lymphoma after two or more systemic therapies that include a Bruton tyrosine kinase (BTK) inhibitor. The therapy recommendations include a reference to a patient-individual therapy, which should take into account in particular the response under the prior therapies as well as the general condition (age, comorbidities, organ function) of the patients.

Patients who are in good general condition and had a long remission after (immuno)chemotherapy in the previous line of therapy can be retreated with

(immuno)chemotherapy. If the patient is not treated with (immuno-)chemotherapy, active ingredients such as lenalidomide, bortezomib, temsirolimus or, under certain conditions, renewed treatment with ibrutinib can be considered according to guidelines, the written statement of the scientific-medical societies or the AkdÄ and the assessment of clinical experts. Autologous or allogeneic stem cell transplant is primarily performed in the first or second line of therapy. However, for patients who have not yet received a stem cell transplant, this can also be considered in the present treatment setting if there is a good response and an appropriate general condition. If autologous stem cell transplant was previously performed, allogeneic stem cell transplant should be considered in relapse if suitable. Overall, patient-individual therapy, taking into account the response and duration of remission of prior therapies and the general condition, if possible including allogeneic or autologous stem cell transplant is thus considered a suitable comparator for the routine practice data collection.

Individual components of the combination chemotherapies recommended in guidelines are not approved in the present indication. These include cisplatin, bortezomib, fludarabine and rituximab. In addition, bortezomib is not approved as monotherapy and bendamustine and lenalidomide are only approved as monotherapy for the present therapeutic indication. There is a discrepancy between medicinal products approved in the indication and those used in health care/recommended by the guidelines. Fludarabine and rituximab can be prescribed within the framework of Annex VI of the Pharmaceuticals Directive in the present therapeutic indication.

Of the treatment options mentioned in the guidelines and clinical experts, the following therapies are considered suitable comparators in the context of the routine practice data collection and evaluations for patient-individual therapy:

- Bendamustine + rituximab
- Bortezomib ± rituximab
- Lenalidomide ± rituximab
- R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
- VRCAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone)
- Ibrutinib
- R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) / R-DHAP (dexamethasone/ high-dose cytarabine/ cisplatin)
- R-BAC (rituximab + bendamustine + cytarabine)
- Temsirolimus
- R-FCM (fludarabine + cyclophosphamide + mitoxantrone + rituximab)
- R-Cb (rituximab + chlorambucil)

Following the rituximab-containing combination therapies, maintenance treatment with rituximab can be carried out if necessary.

In the present NCCN guideline and the written statement of the scientific-medical societies and the AkdÄ, the active ingredient brexucabtagene autoleucel or a CAR-T cell therapy is also specifically mentioned for the treatment setting after prior therapy with a chemoimmunotherapy and a BTK inhibitor. As the present requirement of routine practice data collection and evaluations refers to brexucabtagene autoleucel as an intervention, brexucabtagene autoleucel cannot be a suitable comparator. Other CAR-T cell therapies are currently not approved for the present indication.

In accordance with the aforementioned explanations, data should be collected as part of the routine practice data collection according to Section 35a Paragraph 3b Sentence 1 SGB V for the presently required patient population compared to patient-individual therapy, taking into account the response and duration of remission of the prior therapies and the general condition, if possible including an allogeneic or autologous stem cell transplant (SCT). The comparators considered suitable for the routine practice data collection in the context of a patient-individual therapy are to be taken into account here.

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 question, the patients are in a late line of treatment and have advanced disease. Thus, a major therapeutic goal is to prolong survival time. Therefore, the assessment of overall survival is essential in the present therapeutic indication.

Against the background of the present predominantly pre-treated patient population, great importance is attached to improving the symptomatology and health-related quality of life of the patients. The scientific-medical societies also considered the recording of patient-reported endpoints on symptomatology and health-related quality of life to be relevant.

In the written submission procedure, the pharmaceutical company states that no validated indication-specific measurement instruments are available for mantle cell lymphoma and that the sensitivity of generic instruments is questionable against the background of the heterogeneous course of the mantle cell lymphoma disease.

In the view of the G-BA, an adequate and sufficiently sensitive recording of patient-reported symptomatology and health-related quality of life is feasible using validated measurement instruments that depict specific aspects of the disease of mantle cell lymphoma with sufficient approximation. In this context, it should be examined to what extent the complexity of the assessment of patient-reported endpoints can be kept as low as possible by focusing on the essential factors of symptomatology and health-related quality of life in the present indication.

The registry operators clarified that the collection of patient-reported data on symptomatology and health-related quality of life does not change the non-interventional character of the data collection and that feasibility is not excluded.

Based on the aspects described, the G-BA considers the assessment of symptomatology and health-related quality of life as part of the routine practice data collection to be fundamentally relevant.

In the specific case at hand, however, it is taken into account that so far none of the identified registries is suitable as a primary data source for a routine practice data collection without extensive adaptations and that the recruitment possibilities for the prospective comparator group may be limited.

Based on the available information, it is unclear in which time frame the assessment of patient-reported endpoints on symptomatology and health-related quality of life can be implemented in the identified indication registry. Due to the possibly limited recruitment possibilities for the prospective comparator group and the resulting necessary timely adjustment of the indication registry, limitations may arise within the framework of feasibility.

The pharmaceutical company shall address the necessary adaptations to the identified indication-specific registry when preparing the study protocol and statistical analysis plan. With regard to the implementation of the assessment of patient-reported endpoints on symptomatology and health-related quality of life, the pharmaceutical company shall state:

- whether an adaptation of the identified indication registry to this requirement is possible and within which time frame this can be realised and
- the extent to which the time required for adaptation affects the recruitment opportunities for the prospective comparator group.

The G-BA reserves the right to review whether, after submission of the study protocol and the statistical analysis plan, the requirement to assess patient-reported symptomatology and 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. This weighing decision also takes into account the fact that the main therapeutic goal in the present advanced stage of the disease is to prolong overall survival.

With regard to side effects, the overall rates of serious adverse events (SAEs), serious adverse events and discontinuations due to adverse events should be collected. In addition, defined specific adverse events shall be recorded. The specific AEs should address both brexucabtagene autoleucel and the comparator therapies and ideally be coded using the MedDRA system.

In its written submission, the pharmaceutical company explains that the side effects of the therapy with brexucabtagene autoleucel are subject to much closer monitoring than the other treatment options in the therapeutic indication, thus rendering an unbiased comparison infeasible. According to the statements of the clinical participants in the expert consultation,

a valid recording of side effects is also assessed as possible for the treatment options of the specific comparator. The present patient population includes seriously ill subjects who regularly visit the treatment facility, especially in the case of active disease and occurring side effects. The specified close monitoring of side effects to brexucabtagene autoleucel refers exclusively to the first weeks after infusion and is therefore not considered an obstacle with regard to a consideration of the long-term (additional) benefits and harms of treatment with brexucabtagene autoleucel in the endpoint category of side effects. Specific aspects that may need to be considered in the implementation of routine practice data collection and evaluations due to a different side effect profile of the intervention and comparator can be addressed by the pharmaceutical company when preparing the study protocol and statistical analysis plan. Overall, the G-BA considers it feasible to collect the endpoints of side effects through the observation periods resulting from the provision of care for the intervention and comparator groups without relevant effects of risk of bias that significantly limit the interpretability of the data.

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 collected data, the use of an indication registry is also required in which treatment of relapsed or refractory mantle cell lymphoma is carried out according to everyday German 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, none of the identified registries is suitable as a primary data source for routine practice data collection without extensive adaptations. In the medium term, the European indication-specific EMCL registry may be a suitable primary data source. The adaptations required for the routine practice data collection refer in particular to the following aspects in accordance with the IQWiG[1] concept:

- Significant increase of the target documentation with approaching completeness

- Implementation of the assessment of patient-reported endpoints on symptomatology and health-related quality of life
- Implementation of the assessment of adverse events
- Systematic identification of relevant confounders and expansion of the data set to include previously unrecorded, relevant confounders
- Supplementing the continuous measures to check the quality of the data with IT-supported checks and a query system (systematic clarification of nonconformities); introduce source data verification based on a sample of, e.g. 10% of the data sets

Provided that the quality criteria and requirements of routine practice data collection specified in this resolution can be implemented in the EMCL registry, the EMCL registry is to be used as the primary registry. Regarding the implementation of the assessment of patient-reported endpoints on symptomatology and health-related quality of life, please refer to the explanations in section 2.1.1.

According to Annex I of the ATMP Quality Assurance Guideline, treatment facilities that use the active ingredient brexucabtagene autoleucel are obliged to maintain personnel and structural requirements for connection to the registry modules for CAR-T cells in the German Registry for Stem Cell Transplantation (GRST), the Paediatric Registry for Stem Cell Transplantation (PRST) and the registry of the European Society for Blood and Marrow Transplantation (EBMT) and to document information on prior therapies, side effects, type and duration of response, follow-up therapies and overall survival. In addition, according to the requirements of the European Medicines Agency (EMA), all subjects treated with CAR-T cells must be registered in the EBMT registry. For the present requirement of routine practice data collection and evaluations, it should therefore be examined to what extent the data from other registries on brexucabtagene autoleucel (e.g. EBMT registry) are suitable and can be integrated into the indication-specific registry used.

In the written submission procedure, it was stated that duplicate documentation between the registries should be avoided. During the expert consultation, the registry operators explained that cooperative models are already being developed. Therefore, the G-BA considers a far-reaching avoidance of redundancy of the documentation in the registries to be feasible.

A comparison of two active ingredients without randomisation poses in principle a potentially high risk of bias. Therefore, additional factors with a potentially high risk of bias such as the use of different data sources for the comparator group or data of different quality within one data source should be avoided.

For treatment with brexucabtagene autoleucel, mononuclear cells are removed from the patients by means of leukapheresis and prepared individually for each patient. The production of the medicinal product can therefore take several weeks and the treatment is not available to patients immediately after indication. This delay in the start of therapy does not exist for the treatment options of the specific comparator. Therefore, the time of treatment decision should be chosen as the time of enrolment in the sense of an intention-to-treat principle. For

example, the decision of the tumour board could be used to operationalise the treatment decision.

During the submission procedure, the relevance of including retrospective data was brought out. Taking into account the benefit assessment procedure according to Section 35a SGB V on brexucabtagene autoleucel and the previous set-up of existing registries, it can be assumed that the retrospective data show considerable deficiencies, among other things, with regard to the recording of endpoints on morbidity, health-related quality of life and side effects, the recording of clinically relevant confounders and the possibility of implementing the intention-to-treat (ITT) principle. Thus, the scope and quality of the retrospective data is not considered suitable for inclusion in the present requirement of routine practice data collection and evaluations. Accordingly, only a prospective comparative data collection without recourse to retrospective data can be considered for brexucabtagene autoleucel.

In summary, the study design required for brexucabtagene autoleucel is a non-randomised, prospective comparison versus a comparator determined to be appropriate. This should preferably be conducted as a comparative registry study in the EMCL indication registry.

As described above, extensive adaptations of the EMCL registry are necessary in the present case for the implementation of routine practice data collection. If a comparator registry study is therefore not feasible for the present requirement of routine practice data collection and evaluations, a comparator study using a data platform to be set up specifically for the present routine practice data collection (study-specific data collection) is required as an alternative. All requirements described in the resolution for the routine practice data collection and evaluations must be taken into account in the same way when using a data platform to be set up specifically for the present routine practice data collection (study-specific data collection), unless specified otherwise.

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).

The patients in the present therapeutic indication have already been treated several times and show an advanced clinical picture. A major therapeutic goal is to prolong overall survival. From the results of the pivotal phase II ZUMA-2 study, a possible plateauing for overall survival is evident at the earliest 36 months after inclusion in the ZUMA-2 study. Therefore, routine practice data collection should include a duration of observation of at least 36 months.

As an approximation of the appropriate sample size for the routine practice data collection, a sample size of approx. 190 patients is assumed in the result of an orienting sample size estimate based on the endpoint of overall survival, assuming an equal distribution between intervention and comparator groups. In the submission procedure, it was brought out that in the reality of care in the present therapeutic indication, there is no equal distribution between brexucabtagene autoleucel and the comparator. If the recruitment possibilities for the

comparator arm are limited, the pharmaceutical company can also assume a different distribution between intervention and control arms (e.g. 2:1) for the sample size estimate.

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 eligibility 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. The endpoint of overall survival should be used and the shifted hypothesis boundary should be taken into account in accordance with the procedure in IQWiG's[1] 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.

[1] IQWiG Rapid Report A21-130: Concept for routine practice data collection – brexucabtagene autoleucel.

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

Taking into account the time frame required for preparing the draft, the pharmaceutical company shall submit the final drafts for the study protocol and the statistical analysis plan to the G-BA for approval by 21 December 2022 at the latest prior to carrying out the routine practice data collection.

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 19 August 2022 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 6 months, 18 months, 36 months and 54 months after the time of the start of routine practice data collection to be defined by means of a declaratory resolution.

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 months, 36 months and 54 months after the start 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 21 July 2028 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 Section 35a) 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 28 September 2021 at the subcommittee session and the draft resolution was approved.

At its session on 7 October 2021, the plenum resolved to initiate a procedure for the requirement of a routine practice data collection.

In conjunction with the resolution of 7 October 2021 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 for the purpose of preparing a resolution.

IQWiG's concept was submitted to the G-BA on 31 March 2022. On 1 April 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 29 April 2022.

The expert consultation within the framework of the submission by the expert bodies took place on 24 May 2022.

The evaluation of the written submissions received and of the expert consultation was discussed at the session of the Subcommittee on 12 July 2022, and the proposed resolution was approved.

At its session on 21 July 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Working group Section 35a	20 July 2021 15 September 2021 22 September 2021	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 Medicinal products	28 September 2021	Concluding discussion of the draft resolution
Plenum	7 October 2021	Resolution on the initiation of a procedure for the requirement of a routine practice data collection (amendment of Annex XII of the AM-RL)
Working group Section 35a	18 May 2022	Information on written submissions received, preparation of the expert consultation
Subcommittee on Medicinal Products	24 May 2022	Implementation of the expert consultation
Working group Section 35a	1 June 2022 15 June 2022 22 June 2022 5 July 2022	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	12 July 2022	Concluding discussion of the draft resolution
Plenum	21 July 2022	Resolution on the requirement of routine practice data collection (amendment of Annex XII of the AM-RL)

Berlin, 21 July 2022

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

Prof. Hecken