Gemeinsamer Bundesausschuss

Justification

on the Resolution of the Federal Joint Committee (G-BA) on the Suspension of a Consultation Procedure under Section 35a paragraph 3b SGB V
Brexucabtagene Autoleucel (Relapsed or Refractory B-cell Precursor Acute Lymphoblastic Leukaemia); Requirement of Routine Practice Data Collection and Evaluations

of 20 July 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 brexucabtagene autoleucel received a conditional marketing authorisation (Article 14-a of Regulation (EC) No. 726/2004) from the European Commission (EC) on 14 December 2020. In addition, brexucabtagene autoleucel (Tecartus®) 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 2 September 2022, brexucabtagene autoleucel received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

The approved new therapeutic indication according to the product information is: "Tecartus is indicated for the treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL)."

On the basis of the ongoing or completed studies on brexucabtagene autoleucel 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 brexucabtagene autoleucel:

- Data on patient-relevant endpoints that allow an assessment of the long-term additional benefit and harm of treatment with brexucabtagene autoleucel compared to existing therapeutic alternatives for the approved patient population

The marketing authorisation of brexucabtagene autoleucel for the new therapeutic indication of ALL is based on data from the pivotal, single-arm phase I/II ZUMA-3 study. The study enrolled adults aged 18 years and older with primary refractory disease, with a first relapse within 12 months of first remission, with relapsed or refractory disease after more than two lines of systemic therapy, and with relapsed or refractory disease after stem cell transplantation. Subjects with Philadelphia chromosome-positive disease had to be intolerant to tyrosine kinase inhibitor (TKI) therapy or have relapsed or refractory disease after at least two different TKIs.[1]

In addition, an indirect comparison based on the data of the retrospective cohort SCHOLAR-3 study was submitted supportively for marketing authorisation. Accordingly, the marketing authorisation is not based on direct comparator data with existing therapeutic alternatives for the treatment of relapsed or refractory ALL.[2]

By resolution of 3 November 2023, the G-BA initiates a procedure for the requirement of routine practice data collection according to Section 35a, paragraph 3b, sentence 1 SGB V for the active ingredient brexucabtagene autoleucel in the present indication.

By resolution of 16 March 2023 on the benefit assessment according to Section 35a SGB V, a hint for a non-quantifiable additional benefit was identified for brexucabtagene autoleucel for the present therapeutic indication, as the scientific data did not allow quantification.

The indirect comparison between the ZUMA-3 study and the retrospective data of the SCHOLAR-3 study submitted by the pharmaceutical company for the benefit assessment was subject to considerable uncertainties. In addition, the resulting effect estimator could not be meaningfully interpreted due to the highly selected patient population of the indirect comparison and the unclear representativeness for the patients in the present therapeutic indication. The presented indirect comparison of the ZUMA-3 study with the SCHOLAR-3 study is therefore unsuitable for the benefit assessment.

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,

[1] https://clinicaltrials.gov/ct2/show/record/NCT02614066
[2] https://www.ema.europa.eu/en/medicines/human/EPAR/tecartus

4. the evaluations by the pharmaceutical company according to Section 50, paragraphs 2 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. However, there are no suitable ongoing or planned studies for the question of routine practice data collection.

Based on the above-mentioned question, the G-BA deliberated on the requirements for routine practice data collection and evaluations on the basis of IQWiG's concept and the participation of the expert bodies in the concept.

Regardless of the approved therapeutic indication of brexucabtagene autoleucel, the medicinal product is only used in a very limited patient population with relapsed or refractory B-cell precursor ALL in the German healthcare context. According to the information provided by the Competence Centre (CC) Oncology for the assessment of applications for benefit approval by the SHI for planned inpatient treatments with CAR-T cells[3] and the therapy recommendations of the "German Multicentre Study Group for Adult Acute Lymphoblastic Leukaemia" (GMALL), it is evident that the use of CAR-T cells is only recommended from the second salvage therapy line onwards. In the present submission procedure, it was held that this includes, among other things, the treatment settings of relapse after allogeneic stem cell transplantation, relapses after failure of antibody therapies as well as individual decisions in specific cases. According to the information provided by the pharmaceutical company in the expert consultation, the number of patients treated with brexucabtagene autoleucel in Germany can be assumed to be between 24 and 35 per year. Overall, therefore, taking into account medical treatment practice, there is severely limited recruitability for the brexucabtagene autoleucel arm of routine practice data collection.

For the patient population relevant in the German healthcare context for the use of brexucabtagene autoleucel, only a limited selection of comparator therapies is still available. Antibody therapies (blinatumomab or inotuzumab ozogamicin) and allogeneic stem cell transplantation are usually already used as part of the first salvage therapy in accordance with the therapy recommendations of GMALL. According to clinical experts, blinatumomab or inotuzumab ozogamicin are primarily used as bridging therapy in later salvage therapy lines

3 Competence Centre Oncology of the Medical Services: Information provided by the CC Oncology for the assessment of applications for SHI benefit approval for planned inpatient treatments with CAR-T cells; last revised 10.10.2022

prior to the use of brexucabtagene autoleucel, if these treatment options are still available. It is therefore unclear whether a relevant percentage of patients for whom therapy with blinatumomab or inotuzumab ozogamicin alone is administered can be recruited in the comparator arm. Only conventional chemotherapies or unapproved treatments can be considered as additional possible comparators for routine practice data collection. This additionally restricts the recruitment options for any comparator arm of the routine practice data collection in a relevant way.

It was discussed during the submission procedure that the effect assumptions made by IQWiG in the concept do not correspond to the expected effects in healthcare. Among other things, according to the clinical experts' comments, the comparator arm, particularly inotuzumab ozogamicin and blinatumomab, may have lower event rates in healthcare due to use with lower leukaemia burden and in earlier lines of therapy. In the written submission procedure, the pharmaceutical company submitted a sample size estimate including different effect differences between brexucabtagene autoleucel and the comparator arm as well as different recruitment ratios. From this calculation, which is assessed as comprehensible, it follows that for the scenarios to be assumed as realistic according to the assessment of the G-BA, a disproportionately long recruitment time would result for the routine practice data collection.

In the view of the G-BA, taking into account the aspects presented in the submission procedure regarding the use of brexucabtagene autoleucel in the German healthcare context, the comparator therapies still in question and the scenarios to be assumed as realistic for the required sample size for routine practice data collection, the recruitment of a sufficient number of patients for the routine practice data collection is infeasible within an appropriate study period in the present case.

In the overall assessment, the generation of routine practice data, which would improve the existing evidence base sufficiently for the purpose of the benefit assessment, is considered infeasible in the present case.

Therefore, the G-BA suspends the consultation on the requirement of routine data collection and evaluations for the active ingredient brexucabtagene autoleucel in the treatment of adults aged 26 years and older with relapsed or refractory B-cell precursor ALL.

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 October 2022 at the subcommittee session and the draft resolution was approved.

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

In conjunction with the resolution of 3 November 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 31 March 2023. On 3 April 2023, 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 2 May 2023.

The expert consultation within the framework of the submission by the expert bodies took place on 22 May 2023.

The evaluation of the written submissions received and of the expert consultation was discussed at the session of the Subcommittee on 11 July 2023, and the proposed resolution was approved.

At its session on 20 July 2023, the plenary decided on the suspension of consultations on the requirement of routine practice data collection and evaluations.

Chronological course of consultation

Session	Date	Subject of consultation
WG RPDC	18 July 2022 15 August 2022 12 September 2022 17 October 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 Medicinal products	25 October 2022	Concluding discussion of the draft resolution
Plenum	3 November 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	15 May 2023	Information on written submissions received, preparation of the expert consultation
Subcommittee on Medicinal Products	22 May 2023	Implementation of the expert consultation
WG RPDC	1 June 2023 19 June 2023 6 July 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	11 July 2023	Concluding discussion of the draft resolution
Plenum	20 July 2023	Resolution on the suspension of the consultation procedure on the requirement of routine practice data collection

Berlin, 20 July 2023

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

Prof. Hecken