Gemeinsamer Bundesausschuss

Justification

on the Resolution of the Federal Joint Committee (G-BA) on the Suspension of a Consultation Procedure under Section 35a para. 3b SGB V
Exagamglogene autotemcel (β-thalassaemia); requirement of routine practice data collection and evaluations

of 1 February 2024

Contents

1. Legal basis

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

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

2. Key points of the resolution

The EMA's centralised marketing authorisation procedure for the active ingredient exagamglogene autotemcel started in January 2023. The active ingredient exagamglogene autotemcel was granted orphan designation by the EMA on 17 October 2019 (EU/3/19/2210).

The marketing authorisation and initial listing in the directory services in accordance with Section 131, para. 4 SGB V were still pending at the time the resolution was passed. On 14 December 2023, exagamglogene autotemcel received a positive recommendation from the European Medicines Agency (EMA) for conditional marketing authorisation for the following therapeutic indication: Treatment of transfusion-dependent β-thalassaemia in patients 12 years of age and older for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available.

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

- Data to assess the long-term (additional) benefit and harm of treatment with exagamglogene autotemcel for the patient population included in the marketing authorisation application;
- comparator data of treatment with exagamglogene autotemcel versus existing therapeutic alternatives for the patient population covered by the marketing authorisation application

Only single-arm studies were identified during the study research. On this data basis, it can be assumed that no comparator data are available for treatment with exagamglogene autotemcel compared to existing therapeutic alternatives for the patient population specified by the G-BA and that no improvement in the body of evidence can be expected, taking into account the study planning. Therefore, the G-BA considered it necessary to examine the extent to which the body of evidence for the assessment of the additional benefit of the present medicinal product can be improved by collecting data from healthcare by initiating a procedure for the requirement of routine practice data collection and evaluations.

By resolution of 6 July 2023, the G-BA initiates a procedure for the requirement of a routine practice data collection according to Section 35a, para. 3b, sentence 1 SGB V for the active ingredient exagamglogene autotemcel.

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 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.

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.

The pharmaceutical company stated in the written submission and in the expert consultation that a prospective Post Authorisation Safety Study (PASS) is planned in dialogue with the EMA and the FDA and is to be conducted, among others, in the transplant-specific procedure registry of the European Group for Blood and Marrow Transplantation (EBMT). As part of the

PASS, subjects treated with exagamglogene autotemcel will be followed up for up to 15 years. The comparator arm consists of subjects who receive an allogeneic stem cell transplantation. The concept of the PASS had not yet been finalised at the time of the expert consultation, but according to the pharmaceutical company, the research question of the PASS should include both endpoints on long-term safety and long-term efficacy of the therapy.

Patients for whom an HLA-compatible, related donor is available are excluded from the therapeutic indication of exagamglogene autotemcel, for which a positive recommendation for marketing authorisation has been issued by the EMA. Accordingly, for the majority of the patient population relevant for the routine practice data collection, a curatively intended allogeneic stem cell transplantation is not considered as a comparator therapy, but rather non-curatively intended therapy options (e.g. needs-based transfusion therapy).

The comparator arm of the planned PASS therefore does not reflect all relevant therapy options for the patient population covered by the current marketing authorisation procedure. Furthermore, it is unclear to what extent information on all relevant confounders for a non-randomised comparison is available from the PASS and whether all patient-relevant endpoints required for the benefit assessment are collected in the PASS.

Based on this, the G-BA classifies the PASS planned in collaboration with the regulatory authorities as unsuitable to adequately address the existing evidence gaps for the patient population covered by the applied marketing authorisation for the purpose of the benefit assessment.

Regardless of this, the generation of routine practice data, which would adequately improve the existing body of evidence for the purpose of the benefit assessment, is considered infeasible in the present case. This is justified by the following aspects:

For an adequate confounder control of the routine practice data, at least 100 patients who can be recruited in a routine practice data collection are generally required.

IQWiG's estimation of patient numbers for the therapeutic indication covered by the pharmaceutical company's marketing authorisation application revealed a possible sample size of over 100 patients.[1] Based on this and taking into account the above aspects, a consultation procedure for the requirement of routine practice data collection and evaluations was initiated with the resolution of 6 July 2023.

As part of the submission procedure, the Paul-Ehrlich-Institut pointed out that the therapeutic indication currently under discussion in the marketing authorisation procedure is subject to the limitation that patients must be suitable for haematopoietic stem cell transplantation. This is reflected accordingly in the therapeutic indication for which the EMA issued a positive recommendation for marketing authorisation on 14 December 2023. Based on IQWiG's estimation of the patient numbers in the case of a limitation to patients who must be suitable

[1] Exagamglogene autotemcel (transfusion-dependent ß-thalassaemia); G23-11; estimation of patient numbers; IQWiG, 30 May 2023

for haematopoietic stem cell transplantation, this results in a possible sample size of less than 100 patients.[2]

Accordingly, based on the therapeutic indication on which the recommendation for marketing authorisation is based, it can be assumed that the sample size required for an adequate confounder control cannot be achieved.

In addition, it is unclear to what extent sufficiently significant data on the morbidity endpoint defined in the concept (secondary diseases of the underlying disease or secondary haemochromatosis) in the present therapeutic indication can be collected in a routine practice study. It is to be expected that an observation period of considerably more than three years is required for a valid recording of secondary diseases of the underlying disease or secondary haemochromatosis, for example 15 years as in the PASS described above. However, this would result in a disproportionately long period of routine practice data collection.

In the overall assessment, in the specific case at hand, it does not appear feasible to conduct routine practice data collection within an appropriate study period, mainly due to the assumed sample size of less than 100 patients in the therapeutic indication and the required duration of observation for a sufficiently significant data collection of the relevant morbidity endpoints. The G-BA is therefore suspending the consultation on the requirement of routine practice data collection and evaluations for the active ingredient exagamglogene autotemcel in the treatment of transfusion-dependent β-thalassaemia in patients 12 years and older.

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.

[2] Exagamglogene autotemcel (transfusion-dependent ß-thalassaemia); G23-07; estimation of patient numbers; IQWiG, 02 May 2023

The recommended resolution on the initiation of a procedure for the requirement of a routine practice data collection was discussed on 27 June 2023 at the subcommittee session and the draft resolution was approved.

At its session on 6 July 2023, the plenum resolved to initiate a procedure for the requirement of a routine practice data collection.

In conjunction with the resolution of 6 July 2023 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 6 October 2023. On 9 October 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 6 November 2023.

The expert consultation within the framework of the submission by the expert bodies took place on 27 November 2023.

The evaluation of the written submissions received and of the expert consultation was discussed at the session of the Subcommittee on 23 January 2024, and the proposed resolution was approved.

At its session on 1 February 2024, 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	6 April 2023 4 May 2023 1 June 2023 19 June 2023	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	27 June 2023	Concluding discussion of the draft resolution
Plenum	6 July 2023	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	20 November 2023	Information on written submissions received, preparation of the expert consultation
Subcommittee on Medicinal Products	27 November 2023	Implementation of the expert consultation
WG RPDC	7 December 2023 5 January 2024 15 January 2024	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	23 January 2024	Concluding discussion of the draft resolution
Plenum	1 February 2024	Resolution on the suspension of the consultation procedure on the requirement of a routine practice data collection

Berlin, 1 February 2024

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

Prof. Hecken