Gemeinsamer Bundesausschuss

Justification

on the resolution of the Federal Joint Committee (G-BA) on the initiation of a procedure on the requirement of a routine practice data collection and evaluations according to Section 35a, paragraph 3b SGB V:
Autologous anti-CD-19-transduced CD3+ cells (relapsed or refractory mantle cell lymphoma)

of 7 October 2021

Contents

1. Legal basis

According to Section 35a, paragraph 3b, sentence 9 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). L 136, 30.4.2004, p. 1), as last amended by Regulation (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

With the present resolution, 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 (Tecartus®).

According to Chapter 5, Section 51 of the Rules of Procedure of the G-BA (VerfO), the procedure for the requirement of routine practice data collection and evaluations is divided into

1. the assessment of necessity according to Section 54,
2. the resolution of the plenary session initiating proceedings under Section 55 and evaluations under Section 56,
3. the preparation of a concept for the requirements concerning a routine practice data collection and evaluations with the participation of expert bodies according to Section 57 and
4. the resolution of the plenum demanding a routine practice data collection and evaluations according to Section 58 to be done by the pharmaceutical company.

According to Chapter 5, Section 54 of the VerfO, the initiation of a procedure for the requirement of a routine practice data collection and evaluations prescribes that the routine practice data collection is considered necessary for the purpose of the benefit assessment of a medicinal product. The assessment of necessity is based on documents relating to this medicinal product, in particular from a benefit assessment procedure of the G-BA according to Section 35a SGB V, the marketing authorisation procedure at the European Medicines

Agency (EMA), a request for advice according to Section 7 as well as further documents relating to clinical studies.

The active ingredient autologous anti-CD-19-transduced CD3+ cells (Tecartus®) 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. In addition, the active ingredient autologous anti-CD-19-transduced CD3+ cells (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. The approved therapeutic indication according to the product information is: "Tecartus is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor". The first listing in the directory services in accordance with Section 131, paragraph 4 SGB V, took place on 15 February 2021.

The assessment of the necessity of a routine practice data collection was made based on the ongoing or completed studies on autologous anti-CD-19-transduced CD3+ cells considered for the marketing authorisation, as well as the data submitted for the benefit assessment according to Section 35a SGB V.

The marketing authorisation of autologous anti-CD-19-transduced CD3+ cells is based on data from the pivotal open-label, single-arm Phase II ZUMA-2 study evaluating the safety and efficacy of autologous anti-CD-19-transduced CD3+ cells (KTE-X19) in adult patients with relapsed or refractory mantle cell lymphoma. Patients who received up to five prior therapies, including anthracycline or bendamustine-containing chemotherapy, an anti-CD20 directed monoclonal antibody, and a BTK inhibitor (acalabrutinib or ibrutinib) were included. In support, a meta-analysis of 6 clinical studies was submitted as a historical control as part of the marketing authorisation. In line with the comments in the EPAR[1] , the presented historical comparison was assessed as highly uncertain due to the heterogeneity of the studies used and the questionable representativeness for the study population of the ZUMA-2 study.

Within the framework of the benefit assessment according to Section 35a SGB V, the pharmaceutical company submitted an indirect comparison in the dossier by means of Matching-Adjusted Indirect Comparison (MAIC) based on a meta-analysis of eight external control studies. Based on the analyses presented, a valid causal effect could not be estimated. Among other things, detailed information on the studies used was lacking, and no adequate adjustment could be performed within the MAIC, taking into account all relevant effect modifiers and prognostic factors. It can be assumed that a fitter population is represented in the ZUMA-2 study than in the external control studies.

Furthermore, the pharmaceutical company submitted an indirect comparison to the SCHOLAR-2 study within the framework of the written statement procedure. The SCHOLAR-2 study is a retrospective observational study for which individual patient data were extracted

[1] Tecartus: EPAR – public assessment report (25.01.2021 / EMA/588798/2020)

from patient records in centres in Denmark, Germany, Spain, Italy, Sweden and the UK. Differences in baseline characteristics were present between the relevant patient populations in the SCHOLAR-2 and ZUMA-2 studies, particularly with respect to the number of previous therapy, gender, disease stage, ECOG status, extranodal disease, bone marrow involvement, and presence of B symptoms. Data on the relevant prognostic factors Ki-67, MIPI and morphology were also missing. Overall, the indirect comparison between the ZUMA-2 and SCHOLAR-2 studies was based on considerable uncertainties, which result in particular from the question of sufficient comparability of the study populations and the small sample size of the SCHOLAR-2 study. Moreover, taking into account these uncertainties, the comparative effect estimator was not of the magnitude to derive an effect with sufficient confidence. The indirect comparison was therefore inappropriate for making statements about the extent of the additional benefit.

As part of the post-approval implementation obligations, the pharmaceutical company shall submit the 24-month data of the ZUMA-2 study by 31 March 2022 and a prospective registry study to characterise the long-term efficacy and safety of autologous anti-CD-19-transduced CD3+ cells by 30 June 2042. Furthermore, data from the same registry on long-term efficacy and safety, and in particular on the benefit-risk ratio in female, elderly and severely ill patients, should be submitted by 30 September 2025. As the above claims relate specifically only to the product autologous anti-CD-19-transduced CD3+ cells, it is expected that no comparative data will be collected as part of the obligations to implement post-authorisation measures.

Based on the data justifying the marketing authorisation, the obligations to carry out post-approval measures, and the data submitted for the benefit assessment according to Section 35a SGB V, no comparative data of treatment with autologous anti-CD-19-transduced CD3+ cells versus existing therapy alternatives are available or expected for the approved patient population regarding patient-relevant endpoints. In addition, treatment with autologous anti-CD-19-transduced CD3+ cells represents a novel therapeutic approach, the long-term effects of which cannot be assessed on the basis of the available data, including the potential cure of patients against the background of the highly malignant and advanced disease of the present patient population.

Since therapy alternatives are available in the present therapeutic indication, it is considered possible within the framework of a routine practice data collection to compare data from the provision of autologous anti-CD-19-transduced CD3+ cells with data from the provision of other treatment options in order to improve the evidence base for the benefit assessment.

The G-BA can develop a concept for routine practice data collection itself or commission the Institute for Quality and Efficiency in Health Care (IQWiG) to develop a concept for routine practice data collection. The preparation of a concept should, in principle, not exceed a period of 6 months. In the present case, IQWiG is commissioned to prepare the concept. Given the complexity of the issues to be clarified and for capacity reasons, the preparation of the concept in the present case will exceptionally take more than 6 months. This does not adversely affect the parties to the proceedings.

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 according to Section 35a, paragraph 3b, SGB V, the Subcommittee on Medicinal Products commissioned a working group (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.

The recommended resolution on the initiation of a procedure for the requirement of 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 pursuant to Section 35a, paragraph 3b SGB V.

Chronological course of consultation

Session	Date	Subject of consultation
Working group Section 35a	15 September 2021 22 September 2021	Consultation on the initiation of a procedure for the requirement of a routine practice data collection and evaluations
Subcommittee Medicinal product	28 September 2021	Discussion and consensus on the draft resolution
Plenum	7 October 2021	Resolution

Berlin, 7 October 2021

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

Prof. Hecken