Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Epcoritamab (diffuse large B-cell lymphoma, after ≥ 2 prior therapies)

of 4 April 2024

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V). Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 30 million in the last 12 calendar months. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5 Section 5, paragraphs 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient epcoritamab on 15 October 2023 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 5 October 2023.

Epcoritamab for the treatment of diffuse large B-cell lymphoma (DLBCL), after ≥ 2 prior therapies, is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the approval studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 15 January 2024 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier assessment carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G23-27) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods 1 was not used in the benefit assessment of epcoritamab.

1 General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Epcoritamab (Tepkinly) in accordance with the product information

Tepkinly as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

Therapeutic indication of the resolution (resolution of 4 April 2024):

See the approved therapeutic indication.

2.1.2 Extent of the additional benefit and significance of the evidence

In summary, the additional benefit of epcoritamab is assessed as follows:

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Justification:

For the assessment of the additional benefit of epcoritamab in patients with relapsed or refractory DLBCL, the pharmaceutical company presented data from the pivotal, single-arm phase I/II GCT3013-01 study.

GCT3013-01 study

The GCT3013-01 study is a single-arm, ongoing phase I/II study in adults with various disease entities of relapsed/ refractory (r/r) B-cell lymphoma. The study comprises three separate phases: a dose-finding phase, an expansion phase and a dose-optimisation phase. Enrolled patients could only participate in one of the three study phases. Relevant for the present benefit assessment is the cohort of patients with r/r DLBCL in the expansion phase of the study. In addition to patients with r/r DLBCL, patients with other diseases such as PMBCL, follicular lymphoma or mantle cell lymphoma are also being investigated in this study phase.

Patients with r/r DLBCL in the expansion phase of the study had to have CD20-positive disease and prior therapy with at least two lines of systemic antineoplastic therapy, including at least one anti-CD20 antibody-containing therapy. Patients who were eligible for curative intensive salvage therapy followed by high-dose chemotherapy with haematological stem cell transplantation (HSCT) were not enrolled in the study.

The expansion phase of the GCT3013-01 study is divided into a screening phase, a treatment phase and a follow-up phase. 219 patients were screened in the study for inclusion in the cohort with aggressive non-Hodgkin's lymphoma (aNHL), including DLBCL. Of these, 157 suitable patients were enrolled in the study, 139 of whom were diagnosed with DLBCL. This population forms both the full analysis set (FAS) and the safety population. A clear ITT population cannot be derived due to a lack of information on the number of screened patients with DLBCL and the reasons for exclusion of screened subjects. For the present benefit assessment, the FAS is considered a suitable study population.

The GCT3013-01 study has been conducted at a total of 54 study sites in Australia, North America, Europe and Asia since June 2020 in relation to the aforementioned cohort of the expansion phase relevant for the benefit assessment.

The primary endpoint of the GCT3013-01 study was the overall response rate (ORR), secondary endpoints included the overall survival (OS) and endpoints of the categories of morbidity, health-related quality of life and side effects.

For the study, a total of four data cut-offs were performed:

- 31.01.2022 (data cut-off relevant for the marketing authorisation)
- 30.06.2022 (data cut-off relevant for the marketing authorisation)
- 18.11.2022
- 21.04.2023

According to the information provided by the pharmaceutical company in the written statement procedure for the present benefit assessment, the data cut-off from 21.04.2023 was an event-driven data cut-off on the endpoint of response in the follicular lymphoma cohort, which was submitted to the European Medicines Agency (EMA) as part of the marketing authorisation application for follicular lymphoma. According to the pharmaceutical company, current data on the cohorts with aNHL, including DLBCL, were also requested by the EMA in parallel.

In view of the fact that the data cut-off from 21.04.2023 comprises a longer duration of observation, this data cut-off is used for the benefit assessment of epcoritamab.

<u>On the results of the pivotal GCT3013-01 study:</u>

<u>Mortality</u>

Of 139 patients, 55.4% had died at the time of the data cut-off from 21.04.2023.

An interpretation and assessment of the data on mortality is not possible due to the missing control group. Therefore, no statements on the extent of additional benefit can be derived for the mortality category.

<u>Morbidity</u>

Progression-free survival (PFS)

In the GCT3013-01 study, PFS was collected as a secondary endpoint. PFS was defined as from day 1 of the first treatment cycle to the day of disease progression or death from any cause, whichever occurs first. The day of disease progression was defined as the earliest documented day of progression on which no partial response or complete response is subsequently measured. Disease progression was determined by an independent review committee (IRC) using the Lugano criteria 2014 or the Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) 2016.

The PFS endpoint is a composite endpoint composed of endpoints of the mortality and morbidity categories. The "mortality" endpoint component was assessed as an independent endpoint in the present study via the "overall survival" endpoint. The morbidity component was not assessed on the basis of symptoms according to the operationalisation, but exclusively using imaging procedures.

Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient-relevance of the endpoint PFS. The overall statement on the extent

of the additional benefit remains unaffected by this, as there is no control group, and no statement on the extent of the additional benefit can be derived. The PFS endpoint is presented additionally.

Tumour response

The primary efficacy endpoint "overall response rate (ORR)" is defined as the percentage of subjects who achieve either a complete response (CR) or a partial response (PR) as the best response, based on the IRC assessment according to the Lugano criteria. All other categories ("stable disease", "disease progression" and "not evaluable") were categorised as non-responders. As a secondary endpoint, the ORR was also determined using LYRIC.

The assessment of the response is not based on symptoms, but mainly on imaging procedures as part of the Lugano classification and LYRIC. For this reason, the above-mentioned endpoints are classified as not patient-relevant.

With regard to the therapeutic indication, the endpoint of complete response is an important prognostic factor and relevant for the treatment decision. A complete response associated with a noticeable reduction in disease symptoms for the subject is generally patient-relevant for the benefit assessment. However, the operationalisation presented here is primarily based on imaging procedures. No further information on physical examinations can be found in the study documents and is not included in the Lugano classification or LYRIC. Complete response is not a validated surrogate of a patient-relevant endpoint in the present population covered by the therapeutic indication. Overall, the "complete response" endpoint is therefore assessed as not patient-relevant.

Regardless of this, the results of the GCT3013-01 study for the tumour response endpoint do not allow a statement to be made on the extent of the additional benefit due to the absence of a control group. The endpoint of overall response rate is presented additionally.

Health status

The general health status was assessed in the GCT3013-01 study using the EQ-5D visual analogue scale (VAS).

The results on the general health status showed return rates of < 60% at all post-baseline data collection time points. Against this background, no evaluable data are available for the endpoint "general health status".

Regardless of this, the results of the GCT3013-01 study for the general health status do not allow a statement to be made on the extent of the additional benefit due to the absence of a control group.

Quality of life

Data on health-related quality of life was collected in the GCT3013-01 study using the Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym) questionnaire.

The results of the FACT-Lym showed return rates of < 60% at all post-baseline data collection time points.

Against this background, there is no assessable data on health-related quality of life.

Regardless of this, the results of the GCT3013-01 study for health-related quality of life do not allow a statement to be made on the extent of the additional benefit due to the absence of a control group.

Side effects

Adverse events (AEs) in total

An adverse event occurred in almost all patients (138 out of 139 patients (99.3%)). These are only presented additionally.

Serious adverse events (SAE)

95 out of 139 patients (68.3%) had at least one serious adverse event.

Severe adverse events (CTCAE grade ≥ 3)

At least one severe AE with CTCAE grade ≥ 3 occurred in 96 out of 139 patients (69.1%).

Therapy discontinuation due to adverse events

In 22 patients (15.8%), an adverse event occurred that led to the discontinuation of the study medication.

Specific AEs

Immune system disorders (28.8%) and infections and infestations (29.5 %) occurred as serious adverse events with an incidence ≥ 10% of patients by system organ class (SOC).

Severe adverse events with CTCAE grade ≥ 3 with an incidence ≥ 10% of patients by system organ class (SOC) were blood and lymphatic system disorders (29.5%), infections and infestations (25.2%) and investigations (13.7%).

An adverse event of special interest with an incidence ≥ 10% of patients was cytokine release syndrome (CRS), which occurred as an adverse event, regardless of severity, in 49.6% of patients and as a serious adverse event in 28.8% of patients.

In summary, no conclusions can be drawn on the extent of the additional benefit for the side effects category due to the absence of a control group.

Overall assessment

The data from the label-enabling, single-arm GCT3013-01 study are available for the benefit assessment. No other data and also no indirect comparison are available.

Since no comparator data are available, no statement on the extent of the additional benefit can be made on the basis of these results.

In summary, the extent of the available results is classified as non-quantifiable because the scientific data basis does not permit quantification.

Significance of the evidence

As the study GCT3013-01 study is a phase I/II study without a control arm, a high risk of bias at study and endpoint level is assumed.

In the overall assessment, this results in a hint for a non-quantifiable additional benefit concerning the significance of the evidence.

2.1.3 Summary of the assessment

The present benefit assessment concerns the benefit assessment of the new medicinal product Tepkinly with the active ingredient epcoritamab.

As an orphan drug, epcoritamab received a conditional marketing authorisation as monotherapy for the treatment of adult patients with relapsed or refractory diffuse large B-lymphoma (DLBCL), after two or more lines of systemic therapy.

For the benefit assessment, the pharmaceutical company submits data from the label-enabling, single-arm GCT3013-01 study. No other data and also no indirect comparison are available.

Since no comparator data are available, no statement on the extent of the additional benefit can be made on the basis of these results.

In the overall assessment, the extent of the additional benefit is classified as non-quantifiable since the scientific data does not allow quantification.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

In order to allow consistent consideration of the patient numbers taking into account the most recent resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the therapeutic indication, the patient numbers of tisagenlecleucel (resolution of 15 February 2024) are used. In this regard, in the resolution on the benefit assessment of tisagenlecleucel for appropriately subdivided patient groups, it was based on a patient number of approx. 525 - 1,200 (patients who are eligible for CAR-T cell therapy or stem cell transplantation) and approx. 525 - 700 (patients who are ineligible for CAR-T cell therapy and stem cell transplantation). In the resolution on tisagenlecleucel, the patient numbers were based exclusively on the relevant patient population eligible for CAR-T cell therapy or stem cell transplantation. For the present resolution, taking into account the two patient groups relevant for the present benefit assessment, this results in a total number of approximately 1,050 to 1,900 patients.
In contrast, the number of patients determined by the pharmaceutical company is subject to uncertainty, as the methodological procedure is inadequately described and incomprehensible in some cases. Overall, this is not considered to be a significantly better estimate of patient numbers compared to the most recent resolutions.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Tepkinly (active ingredient: epcoritamab) at the following publicly accessible link (last access: 22 December 2023):

https://www.ema.europa.eu/en/documents/product-information/tepkinly-epar-product-information_en.pdf

Treatment with epcoritamab should only be initiated and monitored by specialists in internal medicine, haematology and oncology, experienced in the treatment of patients with diffuse large B-cell lymphoma (DLBCL).

This medicinal product received a conditional marketing authorisation. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency EMA will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

In accordance with the EMA's requirements for additional risk minimisation measures, the pharmaceutical company must ensure that all healthcare professionals who may prescribe epcoritamab and each subject treated with epcoritamab receive a patient pass containing information on risks associated with cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) as well as a warning for healthcare professionals treating the subjects and the contact details of the healthcare professional prescribing epcoritamab.

The pivotal study GCT3013-01 did not enrol any patients who were eligible for curative intensive salvage therapy followed by high-dose chemotherapy with haematopoietic stem cell transplantation (HSCT).

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 March 2024).

The annual treatment costs shown refer to the first year of treatment.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

Epcoritamab is administered with a dose escalation regimen: In cycle 1, 0.16 mg epcoritamab (step-up dose 1) is given on day 1, 0.8 mg (step-up dose 2) on day 8 and 48 mg (full dose in each case) on day 15 and day 22.

Subsequently, 48 mg epcoritamab is administered weekly in cycles 2 - 3, every 2 weeks in cycles 4 - 9 and every 4 weeks from cycle 10 onwards.

The product information describes that in cycle 1 all patients should receive premedication with diphenhydramine (or equivalent) and paracetamol. In addition, all patients in cycle 1 should receive premedication and post-medication with prednisolone or dexamethasone.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Epcoritamab	Cycle 1 – 3: 4 x per 28-day cycle Cycle 4 – 9: 2 x per 28-day cycle From cycle 10 onwards: 1 x per 28-day cycle	28	1	28

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Epcoritamab	Cycle 1: Day 1: 0.16 mg	Cycle 1: Day 1: 0.16 mg	1 x 4 mg	28	2 x 4 mg 26 x 48 mg
	Cycle 1: Day 8: 0.8 mg	Cycle 1: Day 8: 0.8 mg	1 x 4 mg		
	Cycle 1: Day 15 and 22: 48 mg	Cycle 1: Day 15 and 22: 48 mg	1 x 48 mg		
	Cycle 2 - 3: Day 1, 8, 15 and 22: 48 mg	Cycle 2 - 3: Day 1, 8, 15 and 22: 48 mg			
	Cycle 4 – 9: Day 1 and 15: 48 mg	Cycle 4 – 9: Day 1 and 15: 48 mg			
	From cycle 10 onwards: Day 1:	From cycle 10 onwards:			

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	48 mg	Day 1: 48 mg			

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Epcoritamab 4 mg	1 CII	723.33	€ 2.00	€ 39.42	€ 681.91
Epcoritamab 48 mg	1 SFI	8,340.81	€ 2.00	€ 473.05	€ 7,865.76
SFI = solution for injection; CII = concentrate for injection or infusion solution					

LAUER-TAXE® last revised: 15 March 2024

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I of the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the

version valid on 31 December 2003 applies to the insured.

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were used as a basis (average body weight: 77.7 kg).[2]

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Medicinal product to be assessed							
Epcoritamab							
Premedication							
Prednisolone [3] 100 mg	100 TAB each 20 mg	€ 21.62	€ 2.00	€ 0.82	€ 18.80	16	€ 18.80
Dimetindene (1 mg/10 kg, IV)	5 SFI 4 mg each	€ 23.72	€ 2.00	€ 5.29	€ 16.43	4	€ 32.86
Paracetamol [3] 500 mg – 1,000 mg	10 TAB 500 mg each	€ 2.96	€ 0.15	€ 0.13	€ 2.68	4	€ 2.68 - € 3.01
	10 TAB each 1,000 mg	€ 3.32	€ 0.17	€ 0.14	€ 3.01		
Abbreviations: SFI = solution for injection; TAB = tablets							

[2] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 18 years and older), www.gbe-bund.de

[3] Fixed reimbursement rate

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy

No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

References:

Product information for epcoritamab (Tepkinly); Tepkinly 48 mg solution for injection; last revised: September 2023

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

On 5 October 2023, the pharmaceutical company submitted a dossier for the benefit assessment of epcoritamab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 15 January 2024 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 5 February 2024.

The oral hearing was held on 26 February 2024.

In order to prepare a recommendation for a resolution, 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 representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 26 March 2024, and the proposed resolution was approved.

At its session on 4 April 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	9 January 2024	Information of the benefit assessment of the G-BA
Working group Section 35a	14 February 2024	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	26 February 2024	Conduct of the oral hearing
Working group Section 35a	6 March 2024 20 March 2024	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	26 March 2024	Concluding discussion of the draft resolution
Plenum	4 April 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 4 April 2024

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

Prof. Hecken