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 (new therapeutic indication: follicular lymphoma, after ≥ 2 prior therapies)

of 6 March 2025

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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 all reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment 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 active ingredient epcoritamab (Tepkinly) was listed for the first time on 15 October 2023 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 16 August 2024, epcoritamab 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).

On 13 September 2024, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient epcoritamab with the new therapeutic indication

"Tepkinly as monotherapy is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy."

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The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 16 December 2024 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of epcoritamab compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment 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 data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of epcoritamab.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

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 follicular lymphoma (FL) after two or more lines of systemic therapy.

Therapeutic indication of the resolution (resolution of 6 March 2025):

See the approved therapeutic indication.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy

Appropriate comparator therapy for epcoritamab:

Individualised therapy with selection of

- bendamustine + obinutuzumab followed by obinutuzumab maintenance treatment in accordance with the marketing authorisation,
- lenalidomide + rituximab,
- rituximab monotherapy,
- mosunetuzumab and
- tisagenlecleucel

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

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application, unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

On 1.

The antineoplastic agents bendamustine, bleomycin, carmustine, chlorambucil, cyclophosphamide, cytarabine, doxorubicin, etoposide, methotrexate, mitoxantrone, trofosfamide, vinblastine and vincristine, the glucocorticoids prednisolone and prednisone,

and the radiotherapeutic agent ibritumomab tiuxetan have been approved for the treatment of non-Hodgkin lymphoma. The glucocorticoids dexamethasone and methylprednisolone are also approved.

The PI3K inhibitors idelalisib and duvelisib, the immunomodulator lenalidomide, the monoclonal antibodies epcoritamab, mosunetuzumab, rituximab and obinutuzumab, the Bruton tyrosine kinase inhibitor zanubrutinib and the CAR-T cell therapy tisagenlecleucel have a specific marketing authorisation for the treatment of follicular lymphoma. The CAR-T cell therapy axicabtagene ciloleucel is only approved for the treatment of patients after three or more systemic therapies.

On 2.

In the present therapeutic indication, radiotherapy as well as allogeneic or autologous stem cell transplantation can be considered as non-medicinal treatments. However, it is assumed that neither radiotherapy nor autologous or allogeneic stem cell transplantation is indicated at the time of therapy with epcoritamab for the present treatment setting.

On 3.

Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Zanubrutinib (resolution of 6 June 2024)
- Axicabtagene ciloleucel (resolution of 21 December 2023)
- Mosunetuzumab (resolution of 15 December 2022)
- Tisagenlecleucel (resolution of 1 December 2022)
- Duvelisib (resolution of 21 July 2022)
- Obinutuzumab (resolutions of 4 November 2021)
- Idelalisib (resolution of 19 March 2015)

Annex VI to Section K of the Pharmaceuticals Directive – Prescribability of approved medicinal products in non-approved therapeutic indications (last revised: 28.10.2022):

> Off-label indications for fludarabine:
>
> Fludarabine in combination with cyclophosphamide, mitoxantrone, and rituximab (FCM-R) in eligible patients with lowly or moderately malign non-Hodgkin lymphomas of the B-cell series (CD20 positive NHL, including lymphocytic, lympho-plasmocytic, lymphoplasmacytoid, follicular grade 1 or 2, mantle cell, marginal zone, non-multiple myeloma, non-hair cell leukaemia) and resistance to CHOP (with or without rituximab).

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 indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

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”).

Among the approved active ingredients listed under 1.), only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of care.

The appropriate comparator therapy determined on the basis of this information is explained further below.

Firstly, it should be noted that, irrespective of the fact that grade 3b follicular lymphoma is formally covered by the approved therapeutic indication, the present determination of the appropriate comparator therapy relates to relapsed or refractory grade 1 to 3a follicular lymphoma. This is due to the fact that grade 3b follicular lymphoma is not classified as indolent non-Hodgkin lymphoma according to the generally recognised state of medical knowledge and is treated in the same way as diffuse large B-cell lymphoma (DLBCL). Epcoritamab has a separate marketing authorisation for the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy. This approach is also supported by the new WHO classification 2022[2] of lymphoid tumours, which uses the new term "follicular large cell lymphoma" to distinguish the entity formerly known as "grade 3b follicular lymphoma" from the classic (grades 1 to 3a) follicular lymphoma.

In addition, it is assumed that the patients in the present treatment setting have an indication for systemic antineoplastic therapy due to a correspondingly extensive-stage of the disease, in particular with regard to a symptomatic course (e.g. according to the GELF criteria), and therefore, among other things, a watch-and-wait strategy is not considered.

For the treatment of patients with relapsed or refractory follicular lymphoma, no uniform treatment standard can be derived from the available evidence. The S3 guideline refers to an individualised therapy, which is influenced by various factors, whereby the previous therapy, the course of the disease and the general condition play a special role in the choice of therapy.

According to the S3 guideline, patients with relapse or progression of the disease longer than 2 years after chemoimmunotherapy should be given chemoimmunotherapy again. The guideline also states that obinutuzumab-containing induction therapy and maintenance treatment should be used in patients with rituximab-refractory follicular lymphoma. Obinutuzumab in combination with bendamustine, followed by obinutuzumab maintenance treatment, is the only approved chemoimmunotherapy in this therapeutic indication. Against this background, obinutuzumab in combination with bendamustine, followed by obinutuzumab maintenance treatment in accordance with the marketing authorisation, is determined as a therapy option for individualised therapy.

According to the S3 guideline, monotherapy with rituximab can also be carried out in the relapsed treatment setting, particularly in older or co-morbid patients, if chemoimmunotherapy is unsuitable.

According to the S3 guideline, combination therapy with lenalidomide and rituximab can be used primarily in patients who are refractory or only briefly in remission after chemoimmunotherapy.

According to the written statement of the scientific-medical societies, treatments with CAR-T cell therapies and with the bispecific antibody mosunetuzumab are relevant treatment options in the treatment of relapsed or refractory follicular lymphoma. For the CAR-T cell therapy tisagenlecleucel (resolution of 1 December 2022) and for the bispecific antibody mosunetuzumab (resolution of 15 December 2022), a hint for a non-quantifiable additional benefit was identified in each case in the benefit assessment of orphan drugs because the scientific data did not allow quantification. The period of validity of the resolution on tisagenlecleucel is limited to 1 September 2028. In view of the entire body of evidence,

[2] 2 Allaggio R., Amador C., Anagnostopoulos I., The 5th edition of the World Health Organization Classification of Haematolyphoid Tumours: Lymphoid Neoplasms; Leukaemia (2022)

mosunetuzumab and tisgenlecleucel are determined to be suitable comparators in the context of an individualised therapy.

In addition, the S3 guideline recommends the chemotherapy regimens CHOP (cyclophosphamide + doxorubicin + vincristine + prednisone), CVP (cyclophosphamide + vincristine + prednisone) and MCP (mitoxantrone, chlorambucil, prednisone), each in combination with rituximab, or in the event of a relapse, during or within 6 months of rituximab therapy in combination with obinutuzumab. However, these chemotherapy regimens are not approved in combination with rituximab or obinutuzumab. In the benefit assessment procedure on axicabtagene ciloleucel, the statements of the scientific-medical societies indicate that chemoimmunotherapies containing rituximab generally play a subordinate role particularly for patients who have already relapsed several times as they have already been used in previous lines of treatment for relapse[3]. These chemotherapies or chemoimmunotherapies are therefore not determined as therapy options in the context of individualised therapy as appropriate comparator therapy.

Furthermore, the antineoplastic agents bendamustine, chlorambucil and cyclophosphamide, each as monotherapy, are generally considered in accordance with their authorisation status. However, no recommendation can be derived from the available evidence for these monotherapies, which is why they are unsuitable comparators in the context of an individualised therapy.

The PI3K inhibitors idelalisib and duvelisib are also approved for this therapeutic indication. For idelalisib, it was determined by the G-BA's resolution of 15 March 2015 that an additional benefit over the appropriate comparator therapy was not proven, as the necessary evidence had not been submitted. The written statement from the scientific-medical societies indicates that idelalisib is only recommended in later lines of therapy due to its side effects profile, particularly infections and viraemia. For duvelisib, it was determined by resolution of 21 July 2022 that an additional benefit is not proven. The medicinal product is also not sold in Germany. Idelalisib and duvelisib are therefore not considered as appropriate comparator therapy.

In addition, the active ingredient yttrium-90-ibritumomab tiuxetan is also approved for this therapeutic indication. The active ingredient is not sold in Germany and cannot be considered as an appropriate comparator therapy.

The CAR-T cell therapy axicabtagene ciloleucel is another, relatively new treatment option that has been approved for patients with at least three previous therapies, the therapeutic significance of which cannot yet be conclusively assessed. By resolution of 21 December 2023, it was determined for axicabtagene ciloleucel that an additional benefit for patients with at least three prior therapies was not proven, as no suitable data were available to enable an assessment of the additional benefit. Also in view of the fact that tisagenlecleucel is already available as a CAR-T cell therapy with specific marketing authorisation for the therapeutic indication in question, axicabtagene ciloleucel is not included in the appropriate comparator therapy for the present resolution.

Zanubrutinib in combination with obinutuzumab is approved for the treatment of adult patients with refractory or relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies. It was determined in the benefit assessment that an additional benefit was not proven (resolution of 6 June 2024). Taken together, the therapeutic significance of zanubrutinib in combination with obinutuzumab cannot be conclusively

[3] Benefit assessment procedure on the active ingredient axicabtagene ciloleucel (new therapeutic indication: follicular lymphoma, after ≥ 3 prior therapies) - Federal Joint Committee (g-ba.de)

assessed at present. Zanubrutinib in combination with obinutuzumab is therefore not included in the appropriate comparator therapy for the present resolution.

In summary, an individualised therapy is determined by selecting bendamustine + obinutuzumab followed by obinutuzumab maintenance treatment according to the marketing authorisation, lenalidomide + rituximab, rituximab monotherapy, mosunetuzumab and tisagenlecleucel. The treatment decision is made in particular taking into account the prior therapy, course of the disease and general condition.

For the implementation of individualised therapy in a direct comparator study, it is expected that investigators will have a choice of several treatment options that will allow an individualised treatment decision to be made (multi-comparator study). The individualised treatment decision with regard to the comparator therapy should be made before group allocation (e.g. randomisation). This does not include necessary therapy adjustments in the course of the study (e.g. due to the onset of symptomatology or similar).

If only a single comparator study is presented, the extent to which conclusions can be drawn about a sub-population will be examined as part of the benefit assessment.

Editorial note: The term "individualised therapy" is used instead of previously used terms such as "patient-individual therapy" or "therapy according to doctor's instructions". This harmonises the terms used in the European assessment procedures (EU-HTA).

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

An additional benefit is not proven.

Justification:

For the assessment of the additional benefit of epcoritamab in patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy, the pharmaceutical company presented data from the ongoing pivotal, single-arm, open-label, multicentre GCT3013-01 study of phases 1 and 2 in patients with relapsed, progressive or refractory B-cell lymphoma.

The study is divided into a dose escalation phase, a dose expansion phase and a dose optimisation phase. The dose escalation phase was used to determine the dosage of epcoritamab for the subsequent phases.

Patients with different histological subtypes of B-cell neoplasms according to the World Health Organization 2016[4] or 2008[5] classification, including grade 1 to 3A follicular lymphoma were enrolled in the study. For inclusion in the dose expansion or dose optimisation phase of the study, patients had to have relapsed or refractory, measurable disease after 2 or more prior

[4] Swerdlow SH, Campo E, Pileri SA et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016; 127(20): 2375-2390.
[5] WHO. Tumours of Haematopoietic and Lymphoid Tissues. 2008.

systemic antineoplastic therapies, including at least 1 monoclonal antibody therapy directed against the epitope cluster of differentiation (CD)20.

For the benefit assessment of epcoritamab, the pharmaceutical company presented the sub-population of 86 patients in total with grade 1 to 3A follicular lymphoma from the dose optimisation phase. In addition, the pharmaceutical company presented results on patient-reported endpoints for patients with grade 1 to 3A follicular lymphoma from the dose expansion phase.

The GCT3013-01 study began in June 2018 and is being conducted at study sites in North America, Australia, Europe and Asia.

The primary endpoint of the dose expansion phase of the GCT3013-01 study is the overall response rate. The primary endpoint of the dose optimisation phase is the percentage of patients with grade 2 or higher cytokine release syndrome and cytokine release syndrome of any grade from the 1st administration of epcoritamab up to 7 days after administration of the 2nd full dose of epcoritamab.

Due to the single-arm study design, the GCT3013-01 study presented by the pharmaceutical company does not allow a comparison with the appropriate comparator therapy and is therefore unsuitable for the assessment of the additional benefit.

Conclusion:

The pharmaceutical company used the results of the single-arm GCT3013-01 study for assessment of the additional benefit of epcoritamab. The results of the single-arm study are unsuitable for assessment of the additional benefit as they do not allow a comparison with the appropriate comparator therapy.

Therefore, an additional benefit of epcoritamab as monotherapy for the treatment of adults with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy is not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient epcoritamab.

Tepkinly received a conditional marketing authorisation.

The therapeutic indication assessed here is as follows:

Tepkinly as monotherapy is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

The G-BA determined the appropriate comparator therapy to be:

Individualised therapy with selection of

- bendamustine + obinutuzumab followed by obinutuzumab maintenance treatment in accordance with the marketing authorisation,
- lenalidomide + rituximab,
- rituximab monotherapy,
- mosunetuzumab,
- tisagenlecleucel

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For the assessment of the additional benefit of epcoritamab in patients with relapsed or refractory follicular lymphoma, the pharmaceutical company presented data from the ongoing pivotal, single-arm, open-label, multicentre GCT3013-01 study of phases 1 and 2 in patients with relapsed, progressive or refractory B-cell lymphoma. The results of the single-arm study do not allow a comparison with the appropriate comparator therapy and are unsuitable for the assessment of the additional benefit.

An additional benefit of epcoritamab as monotherapy for the treatment of adults with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy is thus not proven.

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).

The resolution is based on the information from the resolution on the benefit assessment of zanubrutinib in the same therapeutic indication (resolution of 6 June 2024).

This is due to the fact that the information provided by the pharmaceutical company on the number of patients in the SHI target population in the present procedure tends to be underestimated due to restrictive inclusion criteria regarding the presence of a diagnosis of follicular lymphoma (FL) (relating to the lower limit) and due to the percentage of patients with at least 2 FL-specific prior therapies, which is based on a point estimate instead of an available confidence interval (relating to the upper limit).

The information on the number of patients from the procedure for zanubrutinib from 2023 is therefore considered methodologically more appropriate compared to the corresponding estimate available in this procedure.

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: 25 November 2024):

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 follicular lymphoma.

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 will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

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 February 2025).

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 co-morbidities) are not taken into account when calculating the annual treatment costs.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77.7 kg). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916)[6].

In the present therapeutic indication, the product information for obinutuzumab specifies an induction regimen in combination with bendamustine over 6 cycles of 28 days each. Section 5.1 of the product information for obinutuzumab specifies the dose for bendamustine (in combination with obinutuzumab) as 90 mg/m^2. The induction phase is followed by obinutuzumab monotherapy as maintenance treatment once every 2 months for a period of 2 years or until disease progression.

The product information for mosunetuzumab for this therapeutic indication provides for a therapy over 8 cycles of 21 days each, whereby no further treatment cycles are required for patients who show a complete response (CR) after the 8 cycles. Patients who show a partial response (PR) after the 8 cycles are additionally given 9 cycles of treatment (17 cycles in total).

CAR-T cell therapies

Tisagenlecleucel concerns genetically modified, patient's own (autologous) T cells, which are usually obtained by leukapheresis. Since leukapheresis is part of the manufacture of the medicinal product according to Section 4, paragraph 14 Medicinal Products Act, no further costs are incurred in this respect for these active ingredients as treatment options of the appropriate comparator therapy.

Tisagenlecleucel is listed on LAUER-TAXE®, but is only dispensed to appropriate qualified inpatient treatment centres, and administered there. Accordingly, the active ingredient is not subject to the Pharmaceutical Price Ordinance (Arzneimittelpreisverordnung) and no rebates according to Section 130 or Section 130a SGB V apply. The calculation is based on the purchase price of the clinic pack, in deviation from the LAUER-TAXE® data usually taken into account.

Tisagenlecleucel is administered as a single intravenous infusion according to the requirements in the underlying product information.

<u>Treatment period:</u>

<u>Adults with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy</u>

[6] Federal health reporting. Average body measurements of the population (2021, both sexes, 15 years and older: http://www.gbe-bund.de/

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: Day 1, 8, 15 and 22 of a 28-day cycle Cycle 4 – 9: Day 1 and 15 of a 28-day cycle From cycle 10 onwards: Day 1 of a 28-day cycle	13.0	Cycle 1 - 3: 4 Cycle 4 – 9: 2 From cycle 10 onwards: 1	28.0
Appropriate comparator therapy				
Individualised therapy with selection of				
bendamustine + obinutuzumab followed by obinutuzumab maintenance treatment in accordance with the marketing authorisation				
Bendamustine	Induction therapy: Day 1 and 2 of a 28-day cycle	6.0	2	12
Obinutuzumab	Induction therapy: 28-day cycles; Cycle 1: Day 1, 8 and 15 Cycles 2 to 6: Day 1	6.0	Cycle 1: 3 Cycle 2 - 6: 1	8
	Maintenance treatment: 1 x every 2 months[7]	3.2	1	3.2
Lenalidomide + rituximab				
Lenalidomide	Day 1 - 21 of a 28-day cycle	12.0	21	252
Rituximab	Cycle 1: Day 1, 8, 15 and 22 of a 28-day cycle	1.0	4	4
	Cycle 2 – 5: Day 1 of a 28-day cycle	4.0	1	4
Rituximab monotherapy				
Rituximab	1 x every 7 days	4.0	1	4
tisagenlecleucel				
tisagenlecleucel	Single dose	1.0	1	1

[7] One month corresponds to 30.4 days.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Mosunetuzumab				
Mosunetuzumab	Cycle 1: Day 1, 8 and 15 of a 21-day cycle Cycle 2 – 8 or 17: Day 1 of a 21-day cycle	8.0 – 17.0	Cycle 1: 3 Cycle 2 – 8 or 17: 1	10 - 19

Consumption:

For tisagenlecleucel, the consumption of infusion bags is shown according to the requirements in the product information. These are administered to the patient in a single infusion depending on the number of cells per infusion bag. The annual treatment costs of tisagenlecleucel are independent of the specific number of infusion bags used.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment day	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	Cycle 1: Day 1: 1 x 4 mg	28.0	3 x 4 mg + 25 x 48 mg
	Cycle 1: Day 8: 0.8 mg	Cycle 1: Day 8: 0.8 mg	Cycle 1: Day 8: 1 x 4 mg		
	Cycle 1: Day 15 3 mg	Cycle 1: Day 15 3 mg	Cycle 1: Day 15 1 x 4 mg		
	Cycle 1: Day 22: 48 mg	Cycle 1: Day 22: 48 mg	Cycle 1: Day 22: 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 2 - 3: Day 1, 8, 15 and 22: 1 x 48 mg		
	Cycle 4 – 9: Day 1 and 15: 48 mg	Cycle 4 – 9: Day 1 and 15: 48 mg	Cycle 4 – 9: Day 1 and 15: 1 x 48 mg		
	From cycle 10 onwards:	From cycle 10 onwards:	From cycle 10 onwards:		

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment day	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	Day 1: 48 mg	Day 1: 48 mg	Day 1: 1 x 48 mg		
Appropriate comparator therapy					
Individualised therapy with selection of					
bendamustine + obinutuzumab followed by obinutuzumab maintenance treatment in accordance with the marketing authorisation					
Bendamustine	90 mg/m² = 171.9 mg	171.9 mg	1 x 100 mg + 3 x 25 mg	12	12 x 100 mg + 36 x 25 mg
Obinutuzumab	1,000 mg	1,000 mg	1 x 1,000 mg	11.2	11.2 x 1,000 mg
Lenalidomide + rituximab					
Lenalidomide	20 mg	20 mg	1 x 20 mg	252	252 x 20 mg
Rituximab	375 mg/m² = 716.3 mg	716.3 mg	1 x 500 mg + 3 x 100 mg	8	8 x 500 mg + 24 x 100 mg
Rituximab monotherapy					
Rituximab	375 mg/m² = 716.3 mg	716.3 mg	1 x 500 mg + 3 x 100 mg	4	4 x 500 mg + 12 x 100 mg
tisagenlecleucel					
tisagenlecleucel	0.6 - 6 x 10^8 viable CAR+ T cells (regardless of body weight)	0.6 - 6 x 10^8 CAR+ T cells	1 single infusion bag	1	1 single infusion bag
Mosunetuzumab					
Mosunetuzumab	<u>Cycle 1:</u> Day 1: 1 mg Day 8: 2 mg Day 15: 60 mg	<u>Cycle 1:</u> Day 1: 1 mg Day 8: 2 mg Day 15: 60 mg	<u>Cycle 1:</u> Day 1: 1 mg Day 8: 2 x 1 mg Day 15: 2 x 30 mg	10 (8 cycles) – 19 (17 cycles)	3 x 1 mg + 10 x 30 mg – 3 x 1 mg + 19 x 30 mg
	<u>Cycle 2:</u> Day 1: 60 mg	<u>Cycle 2:</u> Day 1: 60 mg	<u>Cycle 2:</u> Day 1: 2 x 30 mg		
	<u>Cycle 3 – 8 or 17:</u> Day 1: 30 mg	<u>Cycle 3 – 8 or 17:</u> Day 1: 30 mg	<u>Cycle 3 – 8 or 17:</u> Day 1: 1 x 30 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 Sections 130 and 130 a 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 reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Adults with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy

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	€ 1.77	€ 39.42	€ 682.14
Epcoritamab 48 mg	1	SFI	€ 8,340.81	€ 1.77	€ 473.05	€ 7,865.99
Appropriate comparator therapy						
Bendamustine 100 mg	5	PIC	€ 1,620.96	€ 1.77	€ 204.07	€ 1,415.12
Bendamustine 100 mg	1	PIC	€ 331.03	€ 1.77	€ 40.46	€ 288.80
Bendamustine 25 mg	5	PIC	€ 414.43	€ 1.77	€ 51.01	€ 361.65
Bendamustine 25 mg	1	PIC	€ 99.39	€ 1.77	€ 11.15	€ 86.47
Lenalidomide 20 mg[8]	63	HC	€ 117.32	€ 1.77	€ 8.38	€ 107.17
Mosunetuzumab 1 mg	1	CIS	€ 275.87	€ 1.77	€ 14.65	€ 259.45
Mosunetuzumab 30 mg	1	CIS	€ 7,751.61	€ 1.77	€ 439.40	€ 7,310.44
Obinutuzumab 1,000 mg	1	CIS	€ 2,649.25	€ 1.77	€ 148.01	€ 2,499.47
Rituximab 500 mg	1	CIS	€ 1,777.34	€ 1.77	€ 98.21	€ 1,677.36
Rituximab 100 mg	2	CIS	€ 717.21	€ 1.77	€ 39.08	€ 676.36

CAR-T cells				
Designation of the therapy	Packaging size	Costs (purchase price clinic pack plus value added tax)	Value added tax (19%)	Costs of the medicinal product
tisagenlecleucel	1 single infusion bag	€ 239,000.00	€ 0 [9]	€ 239,000.00

Abbreviations:
HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; CII = concentrate for injection or infusion solution; PIC = powder for the preparation of an infusion solution concentrate

LAUER-TAXE® last revised: 15 February 2025

[8] Fixed reimbursement rate
[9] The medicinal product is exempt from value added tax at the applied LAUER-TAXE® last revised.

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 5a SGB V, when a non-prescription medicinal product is dispensed invoiced according Section 300, a medicinal product sale price applies to the insured person in the amount of the sale price of the pharmaceutical company plus the surcharges according to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the valid version of 31 December 2003.

Conditioning chemotherapy for lymphocyte depletion under CAR-T cell therapy

Tisagenlecleucel concerns autologous cell products produced from the patient's own T cells. Therefore, a leukapheresis is usually necessary to obtain the cell material. Since leukapheresis is part of the manufacture of the medicinal product pursuant to Section 4, paragraph 14 Medicinal Products Act, no further costs are incurred in this respect for the medicinal product to be assessed and the mentioned active ingredients of the appropriate comparator therapy.

For tisagenlecleucel, provided the white blood cell count is not below ≤ 1,000 cells/µl one week prior to infusion, a treatment regimen for lymphocyte depletion, consisting of intravenous administration of cyclophosphamide (250 mg/m^2 = 477.5 mg) and fludarabine (25 mg/m^2 = 47.8 mg) is given daily for 3 days, with infusion administered 2 to 14 days after the start of lymphocyte depletion.

Screening for hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV)

Patients should be tested for hepatitis B, hepatitis C and HIV infection prior to starting treatment with tisagenlecleucel. Patients receiving therapy with lenalidomide, obinutuzumab and rituximab should be tested for the presence of HBV infection before initiating the respective treatment.

Diagnostics to rule out chronic hepatitis B requires sensibly coordinated steps. A step-by-step serological diagnosis initially consists of the examination of HBs antigen and anti-HBc antibodies. If both are negative, a past HBV infection can be excluded. In certain case constellations, further steps may be necessary in accordance with current guideline recommendations[10].

Diagnostics to rule out hepatitis C requires sensibly coordinated steps. HCV screening is based on the determination of anti-HCV antibodies. In certain case constellations, it may be necessary to verify the positive anti-HCV antibody findings in parallel or subsequently by HCV-

[10] S3 guideline on prevention, diagnosis and therapy of hepatitis B virus infection AWMF registry no.: 021/011 https://register.awmf.org/assets/guidelines/021-011l_S3_Prophylaxe-Diagnostik-Therapie-der-Hepatitis-B-Virusinfektion_2021-07.pdf

RNA detection to confirm the diagnosis of an HCV infection[11].

These examinations are not required for all therapy options of the appropriate comparator therapy. Since there is a regular difference between the medicinal product to be assessed and the appropriate comparator therapy with regard to the tests for hepatitis B, hepatitis C and HIV, the costs of additionally required SHI services are presented in the resolution.

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 Cycle 1							
Prednisolone[8] 100 mg	100 TAB each 20 mg	€ 21.62	€ 1.77	€ 0.82	€ 19.03	16	€ 19.03
Dimetindene (1 mg/10 kg = 7.8 mg), IV	5 SFI 4 mg each	€ 26.24	€ 1.77	€ 7.02	€ 17.45	4	€ 34.90
Paracetamol[8,12] 500 mg – 1,000 mg, PO	10 TAB at 500 mg – 10 TAB at 1,000 mg	€ 2.96 – € 3.32	€ 0.15 – € 0.17	€ 0.13 – € 0.14	€ 2.68 – € 3.01	4	€ 2.68 – € 3.01
Appropriate comparator therapy							
tisagenlecleucel							
Conditioning chemotherapy for lymphocyte depletion							
Cyclophosphamide 250 mg/m² = 477.5 mg, IV	1 PSI at 500 mg	€ 23.50	€ 1.77	€ 1.54	€ 20.19	3	€ 60.57
Fludarabine 25 mg/m² = 47.8 mg	1 CII at 50 mg	€ 118.54	€ 1.77	€ 5.09	€ 111.68	3	€ 335.04

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
HBV screening							
Hepatitis B surface antigen status (GOP 32781)	-	-	-	-	€ 5.06	1	€ 5.06

[11] S3 guideline on prevention, diagnosis and therapy of hepatitis C virus (HCV) infection; AWMF registry no.: 021/012 https://register.awmf.org/assets/guidelines/021-012l_S3_Hepatitis-C-Virus_HCV-Infektion_2018-07.pdf

[12] The dosage of 650 mg paracetamol in premedication stated in the product information cannot be achieved by tablets. Because of this, a dosage of 500 - 1,000 mg is used.

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
Anti-HBc antibody (GOP 32614)	-	-	-	-	€ 5.43	1	€ 5.43
HCV screening							
Hepatitis C HCV antibody status (GOP 32618)	-	-	-	-	€ 9.02	1	€ 9.02
HIV screening							
HIV HIV-1 and HIV-2 antibody status (GOP 32575)	-	-	-	-	€ 4.09	1	€ 4.09
Rituximab							
Premedication for rituximab monotherapy							
Dimetindene (1 mg/10 kg = 7.8 mg), IV	5 SFI 4 mg each	€ 26.24	€ 1.77	€ 7.02	€ 17.45	4	€ 34.90
Paracetamol[8.12] (500 mg - 1,000 mg, PO)	10 TAB at 500 mg – 10 TAB at 1,000 mg	€ 2.96 – € 3.32	€ 0.15 – € 0.17	€ 0.13 – € 0.14	€ 2.68 – € 3.01	4	€ 2.68 – € 3.01
HBV screening for rituximab monotherapy							
Hepatitis B surface antigen status (GOP 32781)	-	-	-	-	€ 5.06	1	€ 5.06
Anti-HBc antibody (GOP 32614)	-	-	-	-	€ 5.43	1	€ 5.43
Premedication for rituximab + lenalidomide							
Dimetindene (1 mg/10 kg = 7.8 mg), IV	5 SFI at 4 mg	€ 26.24	€ 1.77	€ 7.02	€ 17.45	8	€ 69.80
Paracetamol[8.12] (500 mg – 1,000 mg), PO	10 TAB at 500 mg – 10 TAB at 1,000 mg	€ 2.96 – € 3.32	€ 0.15 – € 0.17	€ 0.13 – € 0.14	€ 2.68 – € 3.01	8	€ 2.68 – € 3.01
HBV screening for rituximab + lenalidomide							
Hepatitis B surface antigen status (GOP 32781)	-	-	-	-	€ 5.06	1	€ 5.06
Anti-HBc antibody (GOP 32614)	-	-	-	-	€ 5.43	1	€ 5.43
Bendamustine + obinutuzumab							
HBV screening							
Hepatitis B surface antigen status (GOP 32781)	-	-	-	-	€ 5.06	1	€ 5.06

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
Anti-HBc antibody (GOP 32614)	-	-	-	-	€ 5.43	1	€ 5.43
Mosunetuzumab							
Premedication for the first two cycles							
Dimetindene (1 mg/10 kg = 7.8 mg), IV	5 SFI at 4 mg	€ 26.24	€ 1.77	€ 7.02	€ 17.45	4	€ 34.90
Paracetamol[8.12] (500 mg - 1,000 mg, PO)	10 TAB at 500 mg	€ 2.96	€ 0.15	€ 0.13	€ 2.68	4	€ 2.68
	10 TAB at 1,000 mg	€ 3.32	€ 0.17	€ 0.14	€ 3.01	4	€ 3.01
Dexamethasone[8] (20 mg, IV)	10 SFI at 4 mg	€ 16.92	€ 1.77	€ 0.44	€ 14.71	4	€ 29.42
Abbreviations: SFI = solution for injection; IV = intravenous; CII = concentrate for injection or infusion solution; PSI = powder for solution for injection; PO = per os (oral administration); TAB = tablets							

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1 October 2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

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 requirements 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 follicular lymphoma (FL) 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.

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

At its session on 6 February 2024, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 13 September 2024, 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 2 VerfO.

By letter dated 16 September 2024 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products

with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient epcoritamab.

The dossier assessment by the IQWiG was submitted to the G-BA on 12 December 2024, and the written statement procedure was initiated with publication on the G-BA website on 16 December 2024. The deadline for submitting statements was 6 January 2025.

The oral hearing was held on 27 January 2025.

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 25 February 2025, and the proposed draft resolution was approved.

At its session on 6 March 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	6 February 2024	Determination of the appropriate comparator therapy
Working group Section 35a	14 January 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	27 January 2025	Conduct of the oral hearing
Working group Section 35a	4 February 2025 18 February 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	25 February 2025	Concluding discussion of the draft resolution
Plenum	6 March 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 6 March 2025

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

Prof. Hecken