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 and Annex XIIa – Combinations of Medicinal Products with New Active Ingredients according to Section 35a SGB V Zanubrutinib (New therapeutic indication: follicular lymphoma, after ≥ 2 prior therapies, combination with obinutuzumab)

of 6 June 2024

Contents

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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 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 relevant date for the start of the benefit assessment procedure of the active ingredient zanubrutinib was on 15 December 2023 in accordance with Chapter 5 Section 8, paragraph 1, number 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 2 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 2 VerfO on 08 December 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 15 March 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 zanubrutinib compared to 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

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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 zanubrutinib.

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 Zanubrutinib (BRUKINSA) in accordance with the product information

BRUKINSA in combination with obinutuzumab is indicated for the treatment of adult patients with refractory or relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies.

Therapeutic indication of the resolution (resolution of 6 June 2024):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with refractory or relapsed grade 1 to 3a follicular lymphoma, who have received at least two prior systemic therapies

Appropriate comparator therapy for zanubrutinib in combination with obinutuzumab:

Patient-individual therapy with selection of:

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

taking into account prior therapy, course of the disease and general condition.

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

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

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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.

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

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[2] have been approved for the treatment of non-Hodgkin lymphoma. The glucocorticoids

[2] These active ingredients are currently off the market in Germany.

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dexamethasone and methylprednisolone are also approved. The PI3K inhibitors idelalisib and duvelisib[2], the immunostimulant interferon alfa-2a[2], the immunomodulator lenalidomide, the monoclonal antibodies 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 transplant 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 zanubrutinib 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:

- Axicabtagene ciloleucel (resolution of 21.12.2023)
- Mosunetuzumab (resolution of 15 December 2022)
- Tisagenlecleucel (resolution of 1 December 2022)
- Duvelisib (resolution of 21 July 2022)
- Obinutuzumab (resolution 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 indication 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 leukemia) 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 systematic 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"). Written statements from the German Society for Haematology and Medical Oncology (DGHO) as well as the Drugs Commission of the German Medical Association (AkdÄ) are available.

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 health care provision.

Firstly, it should be noted that, irrespective of the fact that grade 3b follicular lymphoma is formally covered by the currently planned therapeutic indication, it is assumed when determining the appropriate comparator therapy that zanubrutinib is not considered for the treatment of diagnosed grade 3b follicular lymphoma in the

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present therapeutic indication. This sub-entity is not assigned to the indolent non-Hodgkin lymphomas. Accordingly, the new 2022 WHO classification of lymphoid tumours with the new designation "follicular large cell lymphomas" distinguishes the entity formerly known as "follicular lymphoma with grade 3b" from the classic follicular lymphomas (grades 1 to 3a).

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 a patient-individual 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 chemo-immunotherapy 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 patient-individual 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 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 within the scope of orphan drug assessments 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, mosunetuzumab and tisgenlecleucel are determined to be suitable comparators in the context of patient-individual therapy.

In addition, the S3 guideline recommends the chemotherapy regimens CHOP (cyclophosphamide + doxorubicin + vincristine + prednisone), CVP (cyclophosphamide + vincristine + prednisone) and MCP (mitoxantrone, chlorambucin, 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

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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 patient-individual therapy as appropriate comparator therapy.

Furthermore, chemoimmunotherapy with FCM-R (fludarabine in combination with cyclophosphamide, mitoxantrone and rituximab) is a prescribable therapy option in accordance with Annex VI to Section K of the Pharmaceuticals Directive for suitable patients with low or moderately malignant non-Hodgkin lymphomas of the B-cell series, such as grade 1 or 2 follicular lymphoma.

However, fludarabine-containing chemoimmunotherapy is only recommended by the S3 guideline for patients who have been pretreated with chemotherapy without rituximab. In addition, the statements of the scientific-medical societies in the context of the benefit assessment of axicabtagene ciloleucel indicate that fludarabine is only used in individual cases in this therapeutic indication. Against this background, FCM-R is not considered a suitable comparator in the context of patient-individual 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 patient-individual 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.

Idelasisib and duvelisib are therefore not considered as appropriate comparator therapy.

In addition, the active ingredients yttrium-90 ibritumomab tiuxtexan and interferon alfa-2a are also approved for this therapeutic indication. These active ingredients are not sold in Germany and are therefore also not considered as 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

[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)

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ciloleucel is not included in the appropriate comparator therapy for the present resolution.

In summary, no uniform treatment standard can be defined in this therapeutic indication. In accordance with the S3 guideline and the written statements of the scientific-medical societies, treatment decision is made on the basis of patient-individual criteria such as previous treatment, course of the disease and the patient's general condition. Therefore, a patient-individual therapy is determined as an appropriate comparator therapy, taking into account the previous therapy, the course of the disease and the general condition.

The additional benefit should be demonstrated in comparison with several therapy options, which enables a patient-individual treatment decision to be made taking into account the criteria mentioned; as a rule, this should take place within the framework of a multi-comparator study.

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 zanubrutinib is assessed as follows:

Adults with refractory or relapsed grade 1 to 3a follicular lymphoma, who have received at least two prior systemic therapies

An additional benefit is not proven.

Justification:

For the assessment of the additional benefit of zanubrutinib in combination with obinutuzumab compared with the appropriate comparator therapy, the pharmaceutical company submitted the ongoing, open-label, randomised phase II ROSEWOOD study. This study compares zanubrutinib + obinutuzumab with obinutuzumab as monotherapy for follicular lymphoma after at least 2 prior systemic therapies.

Patients were enrolled if they had a histologically confirmed follicular lymphoma of WHO grade 1 to 3a, had previously received chemotherapy (with a CD20 antibody and a combination therapy based on alkylants) and had experienced disease progression after the most recent, at least 2nd line of therapy.

The 217 patients enrolled in the studies were randomised in a 2:1 ratio to a zanubrutinib + obinutuzumab or obinutuzumab arm.

The primary endpoint of the study is overall response. Secondary endpoints include overall survival, progression-free survival, morbidity and health-related quality of life endpoints and adverse events.

The still ongoing study was conducted in study sites in Europe, North America, Australia, New Zealand and Asia and was initiated in November 2017. No information is available on the end of study.

The ROSEWOOD study presented is a single-comparator study in which all patients in the comparator arm received obinutuzumab as monotherapy. Therapy with obinutuzumab as

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monotherapy does not correspond to any of the options specified in the appropriate comparator therapy in the context of a patient-individual therapy. A patient-individual therapy, taking into account previous therapy, the course of the disease and the patient's general condition was also not possible in the study. As a consequence, the appropriate comparator therapy was not implemented in the ROSEWOOD study. On the basis of the study presented, this does not allow any statement to be made on the additional benefit of zanubrutinib in combination with obinutuzumab compared to the appropriate comparator therapy.

In addition, the MAHOGANY study was identified by the pharmaceutical company.

About the MAHOGANY study

This study is a 4-arm randomised, open-label phase III study comparing, among other things, zanubruinib in combination with obinutuzumab with lenalidomide in combination with rituximab in relapsed or refractory follicular lymphoma after at least one prior therapy. This study thus includes a relevant sub-population for the present research question with at least 2 prior therapies. The study is currently in the recruitment phase. According to current estimates, the number of events required for the first interim analysis is likely to be reached by July 2028[4]. Accordingly, no results from the MAHOGANY study are currently available.

In summary, there are no suitable data available to enable an assessment of the additional benefit, which is why an additional benefit of zanubrutinib in combination with obinutuzumab in adult patients with refractory or relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies is not proven.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of zanubrutinib finds its legal basis in Section 35a, paragraph 3, sentence 5 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by the below-mentioned objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

The results of the ROSEWOOD study presented for the assessment of the additional benefit of zanubrutinib are unsuitable for an assessment of the additional benefit of zanubrutinib compared with the appropriate comparator therapy due to the missing implementation of the appropriate comparator therapy.

The first results of the ongoing randomised, controlled MAHOGANY study, which compares, among others, zanubrutinib in combination with obinutuzumab with lenalidomide in combination with rituximab in relapsed or refractory follicular lymphoma after at least one prior therapy, are expected in July 2028[5]. Since clinical data are expected which are relevant for the benefit assessment of the medicinal product, it is justified to limit the validity of the resolution until further scientific knowledge is available for the assessment of the additional benefit of zanubrutinib. The limitation enables the expected results from the MAHOGANY study to be included in the benefit assessment of the medicinal product in accordance with Section 35a SGB V.

[4] Study Details | A Study of Zanubrutinib Plus Anti-CD20 Versus Lenalidomide Plus Rituximab in Participants With Relapsed/Refractory Follicular or Marginal Zone Lymphoma | ClinicalTrials.gov
[5] Study Details | A Study of Zanubrutinib Plus Anti-CD20 Versus Lenalidomide Plus Rituximab in Participants With Relapsed/Refractory Follicular or Marginal Zone Lymphoma | ClinicalTrials.gov

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For this purpose, the G-BA considers a limitation for the resolution until 1 July 2029 to be appropriate.

Conditions of the limitation

For the new benefit assessment after expiry of the deadline, the MAHOGANY study results from the analysis of overall survival and on all other patient-relevant endpoints used for the evidence of an additional benefit are to be presented in the dossier.

A change in the limitation can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long.

In particular, an amendment to the time limit may be granted if an application for marketing authorisation of a new therapeutic indication for zanubrutinib, which includes all or part of the present therapeutic indication, is submitted to the G-BA no later than two months before the expiry of the period of validity of the resolution and an application for an extension of the time limit is submitted on this basis.

In accordance with Section 3 paragraph 7 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 6 VerfO, the procedure for the benefit assessment of the medicinal product with the active ingredient zanubrutinib recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of zanubrutinib (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO). If the dossier is not submitted or is incomplete, the G-BA may determine that an additional benefit is considered as being not proven.

The possibility that a benefit assessment for the medicinal product with the active ingredient zanubrutinib can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1 paragraph 2, nos. 2 – 4 VerfO) remains unaffected hereof.

2.1.5 Summary of the assessment

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

Zanubrutinib in combination with obinutuzumab is indicated for the treatment of adult patients with refractory or relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies.

The G-BA determined the following as appropriate comparator therapy:

Adults with refractory or relapsed grade 1 to 3a follicular lymphoma, who have received at least two prior systemic therapies

A patient-individual therapy with selection of bendamustine + obinutuzumab followed by obinutuzumab maintenance treatment in accordance with the marketing authorisation, lenalidomide + rituximab, rituximab monotherapy, mosunetuzumab and tisagenlecleucel, taking into account the previous therapy, the course of the disease and the general condition.

For the assessment of the additional benefit of zanubrutinib in combination with obinutuzumab compared with the appropriate comparator therapy, the ongoing, open-label, randomised phase II ROSEWOOD study was presented, which compares zanubrutinib + obinutuzumab with obinutuzumab as monotherapy in follicular lymphoma after at least 2 prior systemic therapies. Therapy with obinutuzumab as monotherapy does not correspond to any of the options specified in the appropriate comparator therapy in the context of a patient-individual therapy. A patient-individual therapy, taking into account previous therapy, the course of the disease and the patient's general condition was also not possible in the

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study. Thus, the appropriate comparator therapy was not implemented in the ROSEWOOD study and no statement on the additional benefit of zanubrutinib in combination with obinutuzumab compared to the appropriate comparator therapy can be made on the basis of this study.

In addition, the MAHOGANY study was identified. This study is a 4-arm randomised, open-label phase III study comparing, among other things, zanubruinib in combination with obinutuzumab with lenalidomide in combination with rituximab in relapsed or refractory follicular lymphoma after at least one prior therapy. This study thus includes a relevant sub-population for the present research question with at least 2 prior therapies. However, no results from the MAHOGANY study are currently available.

In summary, there are no suitable data available to enable an assessment of the additional benefit, which is why an additional benefit of zanubrutinib in combination with obinutuzumab in adult patients with refractory or relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies is not proven.

The period of validity of the resolution is limited to 1 July 2029.

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 dossier of the pharmaceutical company.

However, the patient numbers estimated by the pharmaceutical company is subject to uncertainties resulting, for example, from the length of the observation period, ambiguities in the definition of specific follicular lymphoma therapies and a lack of information on the frequency of individual therapies.

In previous procedures in the same therapeutic indication for mosenutuzumab[6] and tisagenlecleucel[7], derivations of the SHI target population for the present therapeutic indication were assessed for the last time. The estimate from the tisagenlecleucel[6] procedure was considered to be a more suitable approximation. Compared to the present procedure for zanubrutinib, the earlier estimate for tisagenlecleucel was based on comparable data. Against the background of the longer observation period, the more up-to-date data and the more detailed information on the demarcation of lines of therapy, the data from the current procedure for zanubrutinib appear more suitable for estimating the size of the SHI target population.

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 Brukinsa (active ingredient: zanubrutinib) at the following publicly accessible link (last access: 13 March 2024):

[6] Benefit assessment procedure for the active ingredient mosunetuzumab (follicular lymphoma, after ≥ 2 prior therapies) - Federal Joint Committee (g-ba.de)
[7] Benefit assessment procedure for the active ingredient tisagenlecleucel (new therapeutic indication: follicular lymphoma, pretreated patients) - Federal Joint Committee (g-ba.de)

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

Treatment with zanubrutinib should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with follicular lymphoma.

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: 1 May 2024).

For the cost representation, one year is assumed for all medicinal products.

The (daily) doses recommended in the product information were used as the calculation basis.

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.

As it is not always possible to achieve the exact target dose per day with the commercially available dose potencies, in these cases rounding up or down to the next higher or lower available dose that can be achieved with the commercially available dose potencies as well as the scalability of the respective dosage form.

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.

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

Treatment period:

Adults with refractory or relapsed grade 1 to 3a follicular lymphoma, who have received at least two prior systemic therapies

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Zanubrutinib in combination with obinutuzumab				
Zanubrutinib	Continuously; 1 x daily	365	1	365
Obinutuzumab	Induction therapy: 28-day cycle 1st cycle: Day 1, 8 and 15 Cycle 2 - 6: Day 1	6	Cycle 1: 3 days Cycle 2 – 6: 1 day	8
	Maintenance treatment: 1 x every 56 days	3	1	3
Appropriate comparator therapy				
Bendamustine + obinutuzumab				
Bendamustine	Induction therapy: Day 1 and 2 of a 28-day cycle	6	2	12
Obinutuzumab	Induction therapy: 28-day cycles; Cycle 1:Day 1, 8 and 15 Cycles 2 to 6: Day 1	6	Cycle 1: 3 Cycle 2 - 6: 1	8
	Maintenance treatment: every 56 days	3	1	3
Lenalidomide + rituximab				
Lenalidomide	Day 1 - 21 of a 28-day cycle	12	21	252
Rituximab	Induction therapy: Day 1, 8, 15 and 22 of a 28-day cycle	1	4	4
	Maintenance treatment: Day 1 of a 28-day cycle	4	1	4
Rituximab monotherapy				
Rituximab	1 x weekly for 4 weeks	4	1	4

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Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Tisagenlecleucel				
Tisagenlecleucel	Single dose	1	1	1
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 - 17	Cycle 1: 3 Cycle 2 – 8 or 17: 1	10 - 19

Consumption:

Adults with refractory or relapsed grade 1 to 3a follicular lymphoma, who have received at least two prior systemic therapies

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).[8]

The consumption of vials and infusion bags is presented for axicabtagene ciloleucel and tisagenlecleucel 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 vial or infusion bag. The annual treatment costs of tisagenlecleucel are independent of the specific number of vials or 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					
Zanubrutinib in combination with obinutuzumab					
Zanubrutinib	320 mg	320 mg	4 x 80 mg	365.0	1460.0 x 80 mg
Obinutuzumab	1,000 mg	1,000 mg	1 x 1,000 mg	11.0	11 x 1,000 mg
Appropriate comparator therapy					
Bendamustine + obinutuzumab					
Bendamustine	90 mg/m² = 171.9 mg	171.9 mg	1 x 100 mg + 3 x 25 mg	12.0	12 x 100 mg + 36 x 25 mg

8 Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older): http://www.gbe-bund.de/

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Designation of the therapy	Dosage/ application	Dose/ patient/ treatment day	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Obinutuzumab	1,000 mg	1,000 mg	1 x 1,000 mg	11.0	11 x 1,000 mg
Lenalidomide + rituximab					
Lenalidomide	20 mg	20 mg	1 x 20 mg	252.0	252 x 20 mg
Rituximab	375 mg/m² = 716.3 mg	716.3 mg	1 x 500 mg + 3 x 100 mg	8.0	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	4.0	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 viable CAR+ T cells	1 single infusion bag	1.0	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	10.0 (8 cycles) – 19.0 (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		

<u>Costs:</u>

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.

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Costs of the medicinal products:

Adults with refractory or relapsed grade 1 to 3a follicular lymphoma, who have received at least two prior systemic therapies

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					
Zanubrutinib 80 mg	120 HC	€ 5,876.35	€ 2.00	€ 332.31	€ 5,542.04
Obinutuzumab 1,000 mg	1 CIS	€ 2,649.25	€ 2.00	€ 148.01	€ 2,499.24
Appropriate comparator therapy					
Bendamustine 100 mg	5 PCI	€ 1,620.96	€ 2.00	€ 204.07	€ 1,414.89
Bendamustine 100 mg	1 PCI	€ 331.03	€ 2.00	€ 40.46	€ 288.57
Bendamustine 25 mg	5 PCI	€ 414.43	€ 2.00	€ 51.01	€ 361.42
Bendamustine 25 mg	1 PCI	€ 99.39	€ 2.00	€ 11.15	€ 86.24
Lenalidomide 20 mg	63 HC	€ 117.32	€ 2.00	€ 8.38	€ 106.94
Mosunetuzumab 1 mg	1 CIS	€ 275.87	€ 2.00	€ 14.65	€ 259.22
Mosunetuzumab 30 mg	1 CIS	€ 7,751.61	€ 2.00	€ 439.40	€ 7,310.21
Obinutuzumab 1,000 mg	1 CIS	€ 2,649.25	€ 2.00	€ 148.01	€ 2,499.24
Rituximab 500 mg	1 CIS	€ 1,777.34	€ 2.00	€ 84.18	€ 1,691.16
Rituximab 100 mg	2 CIS	€ 717.21	€ 2.00	€ 33.50	€ 681.71
Abbreviations: HC = hard capsules, CIS = concentrate for the preparation of an infusion solution, PIC = powder for the preparation of an infusion solution concentrate					
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

LAUER-TAXE® last revised: 01 May 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

9 The medicinal product is exempt from value added tax at the applied LAUER-TAXE® last revised.

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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.

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 = 475 mg) and fludarabine (25 mg/m^2 = 47.5 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, rituximab and zanubrutinibshould 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-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.

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

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

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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							
Zanubrutinib + obinutuzumab							
HBV screening							
Hepatitis B surface antigen status (GOP 32781)	-	-	-	-	€ 5.50	1.0	€ 5.50
Anti-HBc antibody (GOP 32614)	-	-	-	-	€ 5.90	1.0	€ 5.90
Appropriate comparator therapy							
Tisagenlecleucel							
Conditioning chemotherapy for lymphocyte depletion							
Cyclophosphamide 250 mg/m^2 = 477.5 mg	10 PSI at 200 mg	€ 62.80	€ 2.00	€ 2.85	€ 57.95	3.0	€ 57.95
Fludarabine 25 mg/m^2 = 47.8 mg	1 CII at 50 mg	€ 118.54	€ 2.00	€ 5.09	€ 111.45	3.0	€ 334.35
HBV screening							
Hepatitis B surface antigen status (GOP 32781)	-	-	-	-	€ 5.50	1.0	€ 5.50
Anti-HBc antibody (GOP 32614)	-	-	-	-	€ 5.90	1.0	€ 5.90
HCV screening							
Hepatitis C HCV antibody status (GOP 32618)	-	-	-	-	€ 9.80	1.0	€ 9.80
HIV screening							
HIV HIV-1 and HIV-2 antibody status (GOP 32575)	-	-	-	-	€ 4.45	1.0	€ 4.45
Rituximab							
Premedication for rituximab monotherapy							
Dimetindene (1 mg/10 kg, IV)	5 SFI at 4 mg	€ 23.72	€ 2.00	€ 5.29	€ 16.43	4.0	€ 32.86
Paracetamol[9] (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	4.0	€ 2.68 – € 3.01
HBV screening for rituximab monotherapy							
Hepatitis B surface antigen status (GOP 32781)	-	-	-	-	€ 5.50	1.0	€ 5.50

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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)	-	-	-	-	€ 5.90	1.0	€ 5.90
Premedication for rituximab + lenalidomide							
Dimetindene (1 mg/10 kg, IV)	5 ILO at 4 mg	€ 23.72	€ 2.00	€ 5.29	€ 16.43	8.0	€ 65.72
Paracetamol[9] (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	8.0	€ 2.68 – € 3.01
HBV screening for rituximab + lenalidomide							
Hepatitis B surface antigen status (GOP 32781)	-	-	-	-	€ 5.50	1.0	€ 5.50
Anti-HBc antibody (GOP 32614)	-	-	-	-	€ 5.90	1.0	€ 5.90
Bendamustine + obinutuzumab							
HBV screening							
Hepatitis B surface antigen status (GOP 32781)	-	-	-	-	€ 5.50	1.0	€ 5.50
Anti-HBc antibody (GOP 32614)	-	-	-	-	€ 5.90	1.0	€ 5.90
Mosunetuzumab							
Premedication for the first two cycles							
Dimetindene (1 mg/10 kg, IV)	Cycle 1 – 2 (regular) [12]						
	5 ILO at 4 mg	€ 23.72	€ 2.00	€ 5.29	€ 16.43	4.0	€ 32.86
Paracetamol[9] (500 mg - 1,000 mg, PO)	Cycle 1 – 2 (regular)						
	10 TAB at 500 mg	€ 2.96	€ 0.15	€ 0.13	€ 2.68	4.0	€ 2.68
	10 TAB at 1,000 mg	€ 3.32	€ 0.17	€ 0.14	€ 3.01	4.0	€ 3.01
Dexamethasone[9] (20 mg, IV)	Cycle 1 – 2 (regular) [12]						
	10 AMP at 4 mg	€ 16.92	€ 2.00	€ 0.44	€ 14.48	4.0	€ 28.96

Abbreviations:
SFI = solution for injection; INF = infusion solution; CII = concentrate for injection or infusion solution; TAB = tablets; PSI = powder for solution for injection

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Other SHI benefits:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 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 do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (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

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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.

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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.

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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 refractory or relapsed grade 1 to 3a follicular lymphoma, who have received at least two prior systemic therapies

Each of the designated medicinal products is an active ingredient that is specifically named as a concomitant active ingredient in the product information for the assessed medicinal product. Corresponding text extract from the product information for the assessed medicinal product:

"BRUKINSA in combination with obinutuzumab is indicated for the treatment of adult patients with refractory or relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies".

For the designated medicinal products, the requirements of Section 35a, paragraph 3, sentence 4 SGB V are also fulfilled.

References:
Product information for zanubrutinib (BRUKINSA); BRUKINSA 80 mg hard capsules; last revised: 15 April 2024

Supplement to Annex XIIa of the Pharmaceuticals Directive

Since the resolution under I.5 mentions medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V, which can be used in a combination therapy with the assessed active ingredient in the therapeutic indication of the resolution, the information on this designation is to be added to Annex XIIa of the Pharmaceuticals Directive and provided with patient-group-related information on the period of validity of the designation.

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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 3 May 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 12 December 2023.

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

By letter dated 11 December 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits 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 zanubrutinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 March 2024, and the written statement procedure was initiated with publication on the G-BA website on 15 March 2024. The deadline for submitting statements was 5 April 2024.

The oral hearing was held on 22 April 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 28 May 2024, and the proposed resolution was approved.

At its session on 6 June 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

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Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	3 May 2023	Implementation of the appropriate comparator therapy
Subcommittee Medicinal products	12 December 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	17 April 2024	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	22 April 2024	Conduct of the oral hearing
Working group Section 35a	30 April 2024 15 May 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	28 May 2024	Concluding discussion of the draft resolution
Plenum	6 June 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 06 June 2024

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

Prof. Hecken

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