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) Zanubrutinib (new therapeutic indication: marginal zone lymphoma (MZL), after min. 1 prior anti-CD20 therapy)

of 15 June 2023

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. 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 zanubrutinib (Brukinsa) was listed for the first time on 15 December 2021 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 12 August 2022, the pharmaceutical company submitted an application for postponement of the date for the start of the benefit assessment procedure for zanubrutinib in the therapeutic indication "marginal zone lymphoma" in accordance with Section 35a, paragraph 5b SGB V. In its session on 6 October 2022, the G-BA approved the application to postpone the relevant date in accordance with Section 35a, paragraph 5b SGB V. The benefit assessment of zanubrutinib in the therapeutic indication of marginal zone lymphoma begins at the same time as the benefit assessment of zanubrutinib in the therapeutic indication of chronic lymphocytic leukaemia, at the latest within four weeks after marketing authorisation of the therapeutic indication of marginal zone lymphoma according to Chapter 5, Section 8,

paragraph 2 of the Rules of Procedure (VerfO), at the latest six months after the first relevant time point (4 weeks after marketing authorisation of the therapeutic indication of chronic lymphocytic leukaemia).

On 15 November 2022, zanubrutinib received extension of the marketing authorisation for the therapeutic indication of chronic lymphocytic leukaemia. The extension of the marketing authorisation for the therapeutic indication of marginal zone lymphoma was granted on 28 October 2022. Both extensions of the marketing authorisation are 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 12 December 2022, the pharmaceutical company has submitted a dossier 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 zanubrutinib with the new therapeutic indication of marginal zone lymphoma in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 March 2023 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 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 as monotherapy is indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy.

1 General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Therapeutic indication of the resolution (resolution of 15 June 2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with marginal zone lymphoma who have received at least one prior anti-CD20 therapy

Appropriate comparator therapy for zanubrutinib:

Patient-individual therapy with selection of:

- Bendamustine
- CHOP (cyclophosphamide + doxorubicin + vincristine + prednisone)
- CVP (cyclophosphamide + vincristine + prednisone)
- FCM (fludarabine + cyclophosphamide + mitoxantrone) + rituximab (in subjects with resistance to CHOP)
- Chlorambucil
- Cyclophosphamide

taking into account the prior therapy, the course of the disease (including duration of remission since prior therapy) and the general condition

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

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.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. There is no medicinal product with an explicit marketing authorisation for the treatment of marginal zone lymphoma. Marginal zone lymphomas are classified as indolent non-Hodgkin lymphomas. Accordingly, bendamustine, bleomycin,

chlorambucil, cyclophosphamide, cytarabine, dexamethasone, doxorubicin, etoposide, methotrexate, methylprednisolone, mitoxantrone, prednisolone, prednisone, trofosfamide, vinblastine and vincristine are available in the present therapeutic indication according to the marketing authorisation. Medicinal products with explicit marketing authorisation for the treatment of highly malignant non-Hodgkin lymphoma are not considered here.

on 2. In the present therapeutic indication, radiotherapy, surgical resection (e.g. splenectomy) as well as allogeneic and autologous stem cell transplantation are generally considered as non-medicinal treatments.

on 3. A resolution of the G-BA 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 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 therapeutic indication according to Section 35a, paragraph 7 SGB V.

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.

For the present therapeutic indication, it is assumed that the patients 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.

Furthermore, it is assumed that there is no indication for radiotherapy at the time of therapy and, in addition, that autologous or allogeneic stem cell transplantation is unsuitable at the time of therapy with zanubrutinib.

Adequate prior therapy of the patients, if indicated, is assumed depending on the respective entity, e.g. Helicobacter pylori eradication for extranodal marginal zone lymphoma of the stomach, radiotherapy for nodal marginal zone lymphoma or splenectomy for splenic marginal zone lymphoma.
According to the available guidelines and the written statements of the DGHO e.V. (German Society for Haematology and Medical Oncology), patients with a pretreated marginal zone lymphoma are largely treated according to the recommendations for the treatment of follicular lymphoma (grade 1-3A). Consequently, systemic antineoplastic medicinal treatment is the therapy standard. The present guidelines mention various treatment options for treating recurrent marginal zone lymphoma.[2,3,4,5,6,7]

The treatment decision is usually made, taking into account patient-individual factors, in particular the prior therapy, the course of the disease (e.g. duration of previous remission since prior therapy) and the general condition of the patient. The written statement of the DGHO e.V. also states that the choice of therapy regimen depends on the primary therapy, the duration of previous remission, tolerability and comorbidities. In the present therapeutic indication, the appropriate comparator therapy is therefore a patient-individual therapy with a choice of bendamustine monotherapy, CHOP (cyclophosphamide + doxorubicin + vincristine + prednisone), CVP (cyclophosphamide + vincristine + prednisone), FCM (fludarabine + cyclophosphamide + mitoxantrone) + rituximab (for subjects who are resistant to CHOP) , chlorambucil monotherapy and cyclophosphamide monotherapy, taking into account the prior therapy, the course of the disease (including the duration of remission since prior therapy) and general condition.

For the treatment of marginal zone lymphoma, both approved and non-approved medicinal therapies are mentioned in the present guidelines or by scientific-medical societies and/or the Drugs Commission of the German Medical Association (AkdÄ) according to Section 35a, paragraph 7, sentence 4 SGB V.

However, the following components of the combination chemotherapies recommended in the guidelines or by scientific-medical societies and/or the Drugs Commission of the German Medical Association (AkdÄ) according to Section 35a, paragraph 7, sentence 4 SGB V are not approved for the present indication of marginal zone lymphoma: Fludarabine, idelalisib, ibrutinib, lenalidomide, obinutuzumab,

[2] National Institute for Health and Care Excellence (NICE). Non-Hodgkin lymphoma: diagnosis and management, 2016
[3] National Comprehensive Cancer Network (NCCN). B-Cell Lymphomas, 2021
[4] National Comprehensive Cancer Network (NCCN). Primary Cutaneous Lymphomas, 2021
[5] Alberta Health Services (AHS). Lymphoma, 2019
[6] Prica A et al. Rituximab in Lymphoma and Chronic Lymphocytic Leukaemia: A Practice Guideline, 2017
[7] British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018

rituximab. As stated under criterion 3, there is a resolution of the G-BA on the use of fludarabine for lowly or moderately malignant B-NHL other than that specified in the marketing authorisation as CLL (Annex VI to Section K of the Pharmaceuticals Directive).

Medicinal products that do not have a marketing authorisation for the present indication and whose prescribability in off-label use has also not been recognised by the G-BA in the Pharmaceuticals Directive are generally not considered as appropriate comparator therapy in the narrower sense of Section 2, paragraph 1, sentence 3, Section 12 SGB V according to the statements by the Federal Social Court (FSC) on the judgement of 22 February 2023 (File ref.: B 3 KR 14/21 R).
A discrepancy is identified between medicinal products approved in the indication and those used in healthcare/ recommended by the guidelines.

In the present case, the above-mentioned medicinal products recommended in the guidelines or used in healthcare, which do not have a marketing authorisation for the present indication or not an explicit one, cannot be considered as appropriate comparator therapy in the narrower sense within the meaning of Section 2, paragraph 1, sentence 3, Section 12 SGB V, and should therefore, according to the statements by the FSC (judgement of 22.02.2023, file ref.: B 3 KR 14/21 R), not be used as a comparator therapy for the benefit assessment.

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.

Change of the appropriate comparator therapy

Originally, in addition to the treatment options listed above, the following comparators were also considered suitable comparators in the context of patient-individual therapy, taking into account the evidence and the medical treatment situation:

- Bendamustine + rituximab / obinutuzumab
- CHOP (cyclophosphamide + doxorubicin + vincristine + prednisone) + rituximab
- CVP (cyclophosphamide + vincristine + prednisone) + rituximab
- Chlorambucil + rituximab
- Cyclophosphamide + rituximab
- Lenalidomide + rituximab
- Rituximab monotherapy
- Idelalisib
- Ibrutinib

By the present resolution, these treatment options that are not approved in the present therapeutic indication are removed from the selection of patient-individual treatment options.

The change in the appropriate comparator therapy is necessary due to the judgement passed by the Federal Social Court on 22.02.2023, file ref.: D 3 KR 14/21 R, as it considers the designation of medicinal products in off-label use as an appropriate comparator therapy to be fundamentally inadmissible if this does not comply with the requirements of appropriateness in the narrower sense within the meaning of Section 2, paragraph 1, sentence 3, Section 12 SGB V.

The change in the appropriate comparator therapy has no impact on the benefit assessment of zanubrutinib for the treatment of adults with relapsed or refractory marginal zone lymphoma.

2.1.3 Extent and probability of the additional benefit

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

An additional benefit is not proven.

Justification:

For the benefit assessment of zanubrutinib for the treatment of adults with marginal zone lymphoma who have received at least one prior anti-CD20 therapy, the pharmaceutical company submitted the single-arm, phase II MAGNOLIA study and the single-arm, phase I/II BGB-3111-AU-003 study.

<u>MAGNOLIA study</u>

The MAGNOLIA study assessed the efficacy and safety of zanubrutinib in adults with marginal zone lymphoma who have received at least one prior treatment, including at least one CD20-targeted therapy.

The study was conducted from February 2019 to May 2022 in a total of 31 study sites across Asia, Europe, North America, as well as New Zealand and Australia. A total of 68 patients were enrolled in the study.

Patients with histologically confirmed splenic, nodal and extranodal MZL who did not achieve at least a partial response or had documented disease progression after the last systemic therapy were enrolled. The Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of the enrolled patients had to be ≤ 2.

Zanubrutinib was administered orally at a dose of 160 mg in 28-day cycles twice daily until disease progression or unacceptable toxicity.

The primary endpoint of the study was the overall response rate according to the independent review committee. Secondary endpoints comprise endpoints in the categories of morbidity, health-related quality of life and side effects.

Results of individual endpoints from two data cut-offs (from 18.01.2021 and 04.05.2022) were presented.

BGB-3111-AU-003 study

The uncontrolled phase I/II BGB-3111-AU-003 study investigated zanubrutinib in patients with B-cell neoplasms. Twenty patients with relapsed or refractory marginal zone lymphoma were enrolled in the BGB-3111-AU-003 study.

The study was conducted from September 2014 to March 2021 in a total of 24 study sites across Asia, Europe North America, Australia and New Zealand.

In part 1 of the study (dose escalation phase), the recommended zanubrutinib dose for phase II was determined. In part 2 (dose expansion phase), zanubrutinib was assessed at the recommended phase II dose in different histological subtypes of B-cell neoplasms.

Patients with treatment-naive relapsed or refractory marginal zone lymphoma who had received at least one prior systemic therapy were enrolled in the BGB-3111-AU-003 study. 19 (95%) of the patients had received previous rituximab-based chemotherapy. The enrolled patients had to have at least one lymph node suitable for biopsy and an ECOG-PS ≤ 2. Patients who had received prior therapy with a Bruton tyrosine kinase inhibitor and patients who received ongoing treatment with a strong CYP3A inhibitor or inducer were excluded.

Zanubrutinib was administered in treatment cycles of 28 days at a dose of 160 mg twice daily or 320 mg once daily, orally in capsule form until disease progression or unacceptable toxicity occurred.

The primary endpoint of part 2 of the BGB-3111-AU-003 study were endpoints in the category of side effects and, for the patients with MZL, the overall response rate. Secondary endpoints were mortality and endpoints in the morbidity category.

Evaluations were presented for the data cut-off from 31.03.2021.

Overall assessment

For the assessment of the additional benefit of zanubrutinib in adults with marginal zone lymphoma who have received at least one prior therapy with an anti-CD20 antibody, results from the single-arm MAGNOLIA and BGB-3111-AU-003 studies are available.

The results of the submitted single-arm MAGNOLIA and BGB-3111-AU-003 studies are unsuitable for the assessment of additional benefit because they do not allow a comparison with the appropriate comparator therapy, which is why an additional benefit of zanubrutinib in adults with marginal zone lymphoma who have received at least one prior therapy with an anti-CD20 antibody is not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product "Brukinsa" with the active ingredient zanubrutinib.

Zanubrutinib is approved for the treatment of adults with marginal zone lymphoma who have received at least one prior anti-CD20 therapy.
A patient-individual therapy taking into account the prior therapy, the course of the disease (including duration of remission since prior therapy) and the general condition is determined to be the appropriate comparator therapy.
To demonstrate the additional benefit of zanubrutinib compared to the appropriate comparator therapy, the pharmaceutical company submits the single-arm MAGNOLIA and BGB-3111-AU-003 studies. The data presented are unsuitable for comparison with the appropriate comparator therapy.

An additional benefit of zanubrutinib in adults with marginal zone lymphoma who have received at least one prior therapy with an anti-CD20 antibody is therefore 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 G-BA bases its resolution on the patient numbers provided in the dossier by the pharmaceutical company, which are, however, considered to be potentially underestimated.

The pharmaceutical company's calculation is based on data on the incidence and prevalence of non-Hodgkin lymphoma from the Centre for Cancer Registry Data (ZfKD) at the Robert Koch Institute (RKI). Based on 5 - 15% of marginal zone lymphomas in all non-Hodgkin lymphomas, the pharmaceutical company forecasts a lower and an upper limit of the sample size for 2023. In order to determine the percentage of patients for whom a therapeutic indication exists, the pharmaceutical company refers to data from the MZL registry of the University Hospital of Ulm and assumes that a "watch and wait" strategy is indicated for 22% of the patients in the therapeutic indication and, conversely, that 78% of the patients have a marginal zone lymphoma requiring treatment. In order to determine the patients who have received at least one first-line anti-CD20 therapy and require further therapy, the pharmaceutical company uses the percentage of subjects with subsequent therapy after prior anti-CD20 therapy, based on data from the MZL registry.

The resulting information on the number of patients in the target population is considered to be potentially underestimated because patients who were diagnosed before the period under consideration were not taken into account. Furthermore, the percentage of patients for whom a "watch and wait" strategy is not an option is considered to be potentially underestimated, as it only refers to the initial time point and the percentage of patients with an indication for therapy increases over time. Furthermore, the need for therapy was defined by the start of the subsequent therapy. However, the therapeutic indication also includes patients who have not yet received any subsequent therapy despite needing treatment. These patients would have had to be taken into account for the calculation of the upper limit.

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: 1 March 2023):

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 marginal zone lymphoma.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 May 2023).

Treatment period:

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. The recommended total daily dose of zanubrutinib is 320 mg and should be continued until disease progression or unacceptable toxicity.

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	Continuously, 1 x daily or Continuously, 2 x daily	365.0	1.0	365.0
Appropriate comparator therapy				
A patient-individual therapy taking into account the prior therapy, the course of the disease (including duration of remission since prior therapy) and the general condition				
Monotherapies				
Bendamustine	Day 1 and 2 of a 21-day cycle	17.4	2.0	34.8

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Cyclophosphamide	Day 1 of a 21-day cycle	17.4	1.0	17.4
	or			
	Day 1 of a 28-day cycle	13.0	1.0	13.0
Chlorambucil[8]	Day 1 - 5 of a 28-day cycle	13.0	5.0	65.0
R-FCM (fludarabine + cyclophosphamide + mitoxantrone + rituximab) cf. Annex VI to Section K of the Pharmaceuticals Directive				
Fludarabine	Day 1 - 3 of a 28-day cycle	4.0 - 8.0	3.0	12.0 - 24.0
Cyclophosphamide	Day 1 - 3 of a 28-day cycle	4.0 - 8.0	3.0	12.0 - 24.0
Mitoxantrone	Day 1 of a 28-day cycle	4.0 - 8.0	1.0	4.0 - 8.0
Rituximab	Day 1 of a 28-day cycle	4.0 - 8.0	1.0	4.0 - 8.0
CHOP (cyclophosphamide + doxorubicin + vincristine + prednisone) [9]				
Cyclophosphamide	Day 1 of a 21-day cycle	6.0	1.0	6.0
Doxorubicin	Day 1 of a 21-day cycle	6.0	1.0	6.0
Vincristine	Day 1 of a 21-day cycle	6.0	1.0	6.0
Prednisolone[10]	Day 1 - 5 of a 21-day cycle	6.0	5.0	30.0
CVP (cyclophosphamide + vincristine + prednisone) [11]				

[8] Nickenig et al. (2006): German Low-Grade Lymphoma Study Group. Combined cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) improves response rates but not survival and has lower haematologic toxicity compared with combined mitoxantrone, chlorambucil, and prednisone (MCP) in follicular and mantle cell lymphomas: results of a prospective randomised trial of the German Low-Grade Lymphoma Study Group. Cancer. 2006 Sep 1;107(5):1014-22

[9] Flinn IW etal. Randomised trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood. 2014 May 8;123(19):2944-52.

[10] Instead of prednisone, the comparable and less expensive prednisolone was presented due to the principle of economic efficiency.

[11] Sarkozy et al. Risk Factors and Outcomes for Patients With Follicular Lymphoma Who Had Histologic Transformation After Response to First-Line Immunochemotherapy in the PRIMA Trial. J Clin Oncol. 2016 Aug 1;34(22):2575-82.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Cyclophosphamide	Day 1 of a 21-day cycle	8.0	1.0	8.0
Vincristine	Day 1 of a 21-day cycle	8.0	1.0	8.0
Prednisolone[10]	Day 1 - 5 of a 21-day cycle	8.0	5.0	40.0

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916)[12].

For the use of the R-FCM regimen consisting of fludarabine, cyclophosphamide, mitoxantrone and rituximab in the off-label indication "use of fludarabine for lowly or moderately malignant B-non-Hodgkin lymphoma (B-NHL) other than that specified in the marketing authorisation as CLL chronic lymphocytic leukaemia (CLL)", the following dosages are given in Annex VI to the Pharmaceuticals Directive: Fludarabine 25 mg/m² body surface area IV, day 1-3, cyclophosphamide 200 mg/m² body surface area IV, day 1-3, mitoxantrone 8 mg/m² body surface area IV, day 1 and rituximab 375 mg/m² body surface area IV. Day 0. The R-FCM regime is based on a cycle duration of 28 days with a repetition of 4 - 8 cycles.

In a combination of rituximab with cytostatic chemotherapy, CLL patients often showed a - partly also clinically critical - tumour lysis syndrome during the first cycle. Therefore, also in patients with other forms of low-malignant NHL, especially if patients have a high tumour mass, it is recommended that rituximab be administered during the first cycle on day 0 at least 24 hours prior to the start of cytostatic chemotherapy to detect a critical tumour lysis syndrome in time and not to exacerbate it by immediately following administration of cytostatic chemotherapy. Only if no signs of clinically relevant tumour lysis were detected during the previous cycle, the interval between rituximab and cytostatic chemotherapy can be shortened and rituximab can be administered on day 1. In the R-FCM regimen, for patients with high tumour mass, it is recommended that mitoxantrone is not administered during the first cycle, but only when no signs of clinically relevant tumour lysis were evident during the previous cycle.

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.

[12] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/ application	Dose/ patient / treat-ment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Zanubrutinib	320 mg or 160 mg	320 mg	4 x 80 mg	365.0	1460 x 80 mg
Appropriate comparator therapy					
Monotherapies					
Bendamustine	120 mg/m² = 228 mg	228 mg	2 x 25 mg	34.8	69.9 x 100 mg
			2 x 100 mg	34.8	69.9 x 25 mg
Cyclophosphamide	600 - 900 mg/m² = 1,140 mg - 1,710 mg	1140 - 1710 mg	1 x 1,000 mg + 1 x 200 mg – 1 x 1000 mg + 4 x 200 mg	17.4	17.4 x 1,000 mg + 17.4 x 200 mg – 17.4 x 1,000 mg + 69.9 x 200 mg
				13.0	13 x 1,000 mg + 13 x 200 mg – 13 x 1,000 mg + 52 x 200 mg
Chlorambucil [8]	3 x 3 mg/m² = 3 x 5.7 mg = 17.1 mg	17.1 mg	9 x 2 mg	65.0	585 x 2 mg
R-FCM (fludarabine + cyclophosphamide + mitoxantrone + rituximab) cf. Annex VI to Section K of the Pharmaceuticals Directive					
Fludarabine	25 mg/m² = 47.5 mg	47.5 mg	1 x 50 mg	12.0 - 24.0	12 x 50 mg - 24 x 50 mg
Cyclophosphamide	200 mg/m² = 380 mg	380 mg	2 x 200 mg	12.0 - 24.0	24 x 200 mg - 48 x 200 mg
Mitoxantrone	8 mg/m² = 15.2 mg	15.2 mg	1 x 20 mg	4.0 - 8.0	4 x 20 mg - 8 x 20 mg
Rituximab	375 mg/m² = 712.5 mg	712.5 mg	1 x 500 mg 3 x 100 mg	4.0 - 8.0	4 x 500 mg + 12 x 100 mg

Designation of the therapy	Dosage/ application	Dose/ patient / treat-ment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
					– 8 x 500 mg + 24 x 100 mg
CHOP (cyclophosphamide + doxorubicin + vincristine + prednisone)					
Cyclophosphamide	750 mg/m² = 1425 mg	1,425 mg	1 x 1,000 mg + 1 x 500 mg	6.0	6 x 1000 mg + 6 x 500 mg
Doxorubicin	50 mg/m² = 95 mg	95 mg	1 x 100 mg	6.0	6 x 100 mg
Vincristine	1.4 mg/m², max. 2 mg	2 mg	1 x 2 mg	6.0	6 x 2 mg
Prednisolone [10]	100 mg	100 mg	5 x 20 mg	30.0	150 x 20 mg
CVP *(cyclophosphamide + vincristine + prednisone)*					
Cyclophosphamide	750 mg/m² = 1,425 mg	1,425 mg	1 x 1,000 mg + 1 x 500 mg	6.0	6 x 1000 mg + 6 x 500 mg
Vincristine	1.4 mg/m², maximum 2 mg	2 mg	1 x 2 mg	8.0	8 x 2 mg
Prednisolone [10]	100 mg	100 mg	5 x 20 mg	40.0	200 x 20 mg

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Zanubrutinib 80 mg	120 HC	€ 5,995.07	€ 2.00	€ 581.30	€ 5,411.77
Appropriate comparator therapy					
Monotherapies					
Bendamustine 25 mg	5 PIC	€ 374.78	€ 2.00	€ 17.25	€ 355.53

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
Bendamustine 100 mg	5 PIC	€ 1,465.25	€ 2.00	€ 69.00	€ 1,394.25
Cyclophosphamide 200 mg	10 PSI	€ 62.76	€ 2.00	€ 4.89	€ 55.87
Cyclophosphamide 1000 mg	6 PSI	€ 127.41	€ 2.00	€ 11.02	€ 114.39
Chlorambucil 2 mg (+ prednisone)	50 FCT	€ 37.73	€ 2.00	€ 2.51	€ 33.22
R-FCM (fludarabine + cyclophosphamide + mitoxantrone + rituximab) cf. Annex VI to Section K of the Pharmaceuticals Directive					
Fludarabine 25 mg/ml	5 CII	€ 550.82	€ 2.00	€ 25.60	€ 523.22
Cyclophosphamide 200 mg	10 PSI	€ 62.76	€ 2.00	€ 4.89	€ 55.87
Mitoxantrone 20 mg/10 ml	1 CIS	€ 235.54	€ 2.00	€ 10.64	€ 222.90
Rituximab 100 mg	2 CIS	€ 748.07	€ 2.00	€ 69.93	€ 676.14
Rituximab 500 mg	2 CIS	€ 3,639.48	€ 2.00	€ 350.68	€ 3,286.80
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) / CVP (cyclophosphamide + vincristine + prednisone)					
Cyclophosphamide 500 mg	6 PSI	€ 84.41	€ 2.00	€ 9.25	€ 73.16
Cyclophosphamide 1000 mg	6 PSI	€ 127.41	€ 2.00	€ 11.02	€ 114.39
Doxorubicin 100 mg	1 CIS	€ 285.75	€ 2.00	€ 21.71	€ 262.04
Vincristine 1 mg/ml	1 SFI	€ 37.63	€ 2.00	€ 1.25	€ 34.38
Prednisolone 20 mg	100 TAB	€ 21.59	€ 2.00	€ 0.82	€ 18.77
Prednisolone 20 mg	50 TAB	€ 16.89	€ 2.00	€ 0.44	€ 14.45
Abbreviations: FCT = film-coated tablets; HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; CII = concentrate for injection or infusion solution; PII = powder for the preparation of injection or infusion solution; PSI = powder for solution for injection; PIC = powder for the preparation of an infusion solution concentrate; TAB = tablets					

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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.

Diagnosis of hepatitis B infection

Patients should be tested for HBV infection before starting treatment with rituximab. Since there is a regular difference b between the medicinal product to be assessed and the appropriate comparator therapy with regard to the tests for hepatitis, the costs for additionally required SHI services for tests for hepatitis B are presented in the resolution.

Premedication for prevention

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I of the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

In the context of premedication, additionally required SHI services are incurred that usually differ between the medicinal product to be assessed and rituximab (in the combination therapy) as an appropriate comparator therapy and are consequently taken into account as additionally required SHI services 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	Cost/ patient/ year
Appropriate comparator therapy							
R-FCM cf. Annex VI to Section K of the Pharmaceuticals Directive							
HBV diagnostics for rituximab							
HBV test Hepatitis B surface antigen status (GOP number 32781)					€ 5.50	1.0	€ 5.50

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	Cost/ patient/ year
Hepatitis B antibody status (GOP number 32614)					€ 5.90	1.0	€ 5.90
Premedication for rituximab							
Dimetindene IV (1 mg/10 kg, IV)	5 SFI 4 mg each	€ 23.67	€ 2.00	€ 5.81	€ 15.86	4.0 - 8.0	€ 31.72 - € 63.44
Paracetamol (500 mg - 1,000 mg, PO)	10 TAB 500 mg each – 10 TAB 1000 mg each	€ 2.96 – € 3.32	€ 0.15 - € 0.17	€ 0.13 – € 0.14	€ 2.68 – € 3.01	4.0 - 8.0	€ 2.68 - € 3.01
Abbreviations: SFI = solution for injection; TAB = tablets							

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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 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 drugs 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 special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

2.5 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 Zanubrutinib

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.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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 25 January 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 12 December 2022, 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 15 December 2022 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 2023, and the written statement procedure was initiated with publication on the G-BA website on 15 March 2023. The deadline for submitting statements was 5 April 2023.

The oral hearing was held on 2 May 2023.

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 6 June 2023, and the proposed resolution was approved.

At its session on 15 June 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	25 January 2022	Determination of the appropriate comparator therapy
Working group Section 35a	18 April 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	2 May 2023	Conduct of the oral hearing
Working group Section 35a	9 May 2023 30 May 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	6 June 2023	Concluding discussion of the draft resolution
Plenum	15 June 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 June 2023

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

Prof. Hecken