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 (Waldenström's macroglobulinaemia, first-line (unsuitable for chemo-immunotherapy) or after at least 1 prior therapy)

of 16 June 2022

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 relevant date for the first placing on the (German) market of the active ingredient zanubrutinib in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 December 2021. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 14 December 2021.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 15 March 2022, 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 Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy.

Therapeutic indication of the resolution (resolution of 16 June 2022):

"see approved therapeutic indication"

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with Waldenström's macroglobulinaemia who have received at least one prior therapy or adults without prior therapy who are unsuitable for chemo-immunotherapy

Appropriate comparator therapy for zanubrutinib:

- A patient-individual therapy taking into account the general condition and, if applicable, prior therapies and the duration of remission after initial therapy

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

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

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. In addition to zanubrutinib, medicinal products with the following active ingredients are approved in the therapeutic indication:

Bendamustine, chlorambucil, cyclophosphamide, ibrutinib, cytarabine, doxorubicin, mitoxantrone, trofosfamide, vinblastine, vincristine, prednisone, prednisolone and dexamethasone.

Some of the medicinal products listed have a marketing authorisation for the superordinate therapeutic indication "non-Hodgkin lymphoma". Medicinal products with explicit marketing authorisation for the treatment of non-Hodgkin lymphoma of intermediate and high malignancy have not been considered.

on 2. In principle, both allogeneic and autologous stem cell transplant can be considered as non-medicinal therapy in the present therapeutic indication. However, it is assumed that both options are not indicated at the time of therapy with zanubrutinib. Furthermore, plasmapheresis is a relevant non-medicinal therapy option in the therapeutic indication. However, this is usually only used in the short term and with a supportive character in the presence of a hyperviscosity syndrome independently of the antineoplastic therapy and is therefore not included in the appropriate comparator therapy. Regardless of this, patients should be offered plasmapheresis in the context of a clinical study if symptoms of hyperviscosity are present.

on 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Ibrutinib – resolution of 21 July 2016
- Ibrutinib (combination with rituximab) – resolution of 20 February 2020

Annex VI to Section K of the Pharmaceuticals Directive - Prescribability of approved medicinal products in non-approved therapeutic indications (off-label use); part A (last revised 03.03.2022):

- VI. Use of fludarabine in low or intermediate malignant B-non-Hodgkin lymphoma (B-NHL) other than chronic lymphocytic leukaemia (CLL) as specified in the marketing authorisation

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a paragraph 7 SGB V (see “Information on Appropriate Comparator Therapy”). A written statement from the German Society for Haematology and Medical Oncology (DGHO) is 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.

In the available evidence and the written statement of the DGHO on the appropriate comparator therapy, different treatment regimens are recommended for the patient population covered by the present therapeutic indication. On the one hand, the treatment decision depends in particular on the general condition of the subject. On the other, for adults who have already received a prior therapy, prior therapies in particular and the duration of remission after initial therapy also play a role.

Various rituximab-based chemo-immunotherapies are named in both the first-line and second-line of therapies, with re-therapy with the protocol already used in the first-line therapy also being considered depending on the duration of remission. In addition, bortezomib-based treatment regimens and ibrutinib as monotherapy and in combination with rituximab are also considered relevant in the available evidence.

For patients who are not initially eligible for chemo-immunotherapy, primarily due to a reduced general condition, monotherapy with ibrutinib or rituximab in particular are relevant treatment options.

In the overall assessment, the G-BA therefore determines a patient-individual therapy, taking into account the general condition and, if applicable, prior therapies and the duration of remission after initial therapy as an appropriate comparator therapy.

In detail, the active ingredients or combinations of active ingredients bendamustine + rituximab, bortezomib + dexamethasone + rituximab, ibrutinib, ibrutinib + rituximab, rituximab + cyclophosphamide + dexamethasone, bortezomib + rituximab and rituximab are listed as relevant treatment options in the available evidence and the written statement of the DGHO. However, the active ingredients bortezomib and rituximab, with the exception of the combination ibrutinib + rituximab, are not approved for the present indication. Bendamustine is approved exclusively as monotherapy for the treatment of indolent non-Hodgkin lymphoma pretreated with rituximab or rituximab-containing therapies. There is a discrepancy between medicinal therapies approved in the indication and medicinal products used in health care or recommended in guidelines.

For ibrutinib as monotherapy for the treatment of adults with Waldenström's macroglobulinaemia who have received at least one prior therapy or for first-line therapy in adults who are not suitable for chemo-immunotherapy, an additional benefit compared to the appropriate comparator therapy is not proven according to the G-BA resolution of 21 July 2016. For the combination therapy ibrutinib + rituximab, the G-BA resolution of 20 February 2020 also determined that an additional benefit compared to the appropriate comparator therapy is not proven. In both benefit assessment procedures, no suitable data were available to allow an assessment of the additional benefit.

In the context of patient-individual therapy, bendamustine + rituximab, bortezomib + dexamethasone + rituximab, ibrutinib, ibrutinib + rituximab, rituximab + cyclophosphamide + dexamethasone, bortezomib + rituximab and rituximab are considered suitable comparators.

However, the possibility of the off-label use of the active ingredients mentioned in a clinical study does not allow any conclusions to be drawn about their appropriateness in the off-label use in the standard care of insured persons in the SHI system. Such an assessment would be reserved for the decision according to Section 35c SGB V. This does not affect an off-label prescription in specific cases according to the criteria of the established case law of the Federal Social Court on off-label use not regulated in the Pharmaceuticals Directive.

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

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 proof of additional benefit, the pharmaceutical company presented the results of the ongoing, open-label, phase III ASPEN study in the dossier.

The ASPEN study enrolled adults with Waldenström's macroglobulinaemia who had received prior therapy and had relapsed or refractory disease, as well as adults without prior therapy for whom chemo-immunotherapy was not considered appropriate based on medical assessment. All enrolled subjects had to have at least one of the criteria for the indication for therapy of Waldenström's macroglobulinaemia according to the International Workshop on Waldenström's Macroglobulinemia (IWWM)[2] .

The ASPEN study was divided into two cohorts based on the MYD88 mutational status of the adults. Cohort 1 included subjects with a MYD88 mutation and cohort 2 included subjects with wild-type MYD88 or undetermined MYD88 mutational status. Cohort 1 compared the use of zanubrutinib versus ibrutinib monotherapy. Cohort 2 was conducted without a comparator arm.

For the benefit assessment, the pharmaceutical company uses the results of the actively controlled cohort 1. The results of the non-comparator cohort 2 are only presented additionally by the pharmaceutical company. As cohort 2 does not allow for a comparison of zanubrutinib with the appropriate comparator therapy, it is not considered further for the present benefit assessment.

In cohort 1 of the ASPEN study, a total of 201 adults were randomised (zanubrutinib: N = 102; ibrutinib: N = 99). Randomisation was stratified by CXC motif chemokine receptor 4 (CXCR4) mutational status and number of prior therapies.

The treatment with ibrutinib and zanubrutinib was carried out in accordance with the product information. If clinically indicated, plasmapheresis could be performed in the adults for the first two cycles.

The primary endpoint of the study is response rate which includes both complete and very good partial response. Secondary endpoints recorded were overall survival as well as endpoints on morbidity, health-related quality of life and side effects.

The ASPEN study, which has been ongoing since 2017, is being conducted in 60 study sites across Europe, Australia and America. Two data cut-offs were available for the benefit assessment. The first data cut-off of 31 August 2019 is a pre-specified data cut-off ≥ 15 months after 90% of subjects with relapsed or refractory Waldenström's macroglobulinaemia have been enrolled. The second data cut-off from 31 August 2020 was requested by the European Medicines Agency (EMA).

---

[2] Dimopoulos MA, Kastritis E, Owen RG et al. Treatment recommendations for patients with Waldenstrom macroglobulinemia (WM) and related disorders: IWWM-7 consensus. Blood 2014; 124(9): 1404-1411.

On the usability of the study results presented in the dossier

IQWiG stated in the dossier assessment that the results of the ASPEN study presented by the pharmaceutical company in the dossier were incomplete and inadequately prepared. As a result, the IQWiG was unable to adequately assess the study data, so that the results of the study as a whole were not considered usable for the benefit assessment.

In IQWiG's dossier assessment, the overall deficiencies in the dossier are considered to be serious. The finding of incompleteness of content is based specifically on the following deficiencies, described in summary here:

In the dossier, the pharmaceutical company presents evaluations for the 1st data cut-off of 31 August 2019, but not for all relevant patient-reported endpoints. In the ASPEN study, morbidity and health-related quality of life were assessed using the patient-reported endpoints EQ-5D Visual Analogue Scale (VAS) and EORTC QLQ-C30. The pharmaceutical company does not present any results for the VAS of the EQ-5D. In addition, it evaluates only select scales for the EORTC QLQ-C30 (four symptom scales on fatigue, pain, appetite loss, diarrhoea and the global health status scale). However, the study documents show that all 15 scales of the EORTC QLQ-C30 were collected. In the context of the oral hearing on the present benefit assessment procedure, the pharmaceutical company stated that those scales were selectively evaluated in the dossier which the pharmaceutical company considered to be patient-relevant. This procedure is not appropriate since all relevant endpoints collected must be submitted in the dossier according to the dossier template.

Furthermore, the pharmaceutical company does not submit complete subgroup analyses for the data cut-off from 31 August 2019. The pharmaceutical company only considers the treatment status characteristic at the start of the study but does not report any results from an interaction test. The pharmaceutical company justifies the omission of subgroup analyses for further potential effect modifiers as well as interaction testing with the fact that subgroup analyses in the ASPEN study were only defined a priori for the primary endpoint and for the characteristics of gender, age, disease severity or stage as well as the study site and country. In addition, the pharmaceutical company states that no significant effect modification for the primary endpoint could be determined for the investigated characteristics and thus, no effect modification is to be expected for the other endpoints. This procedure is not appropriate, since, according to the dossier templates, subgroup analyses must be submitted for all named effect modifiers for all relevant endpoints according to the criteria specified in the templates, if necessary, also through a post hoc analysis.

The results for the 2nd data cut-off of 31 August 2020 is presented by the pharmaceutical company only descriptively. Here, the evaluations of the patient-reported endpoints are completely missing. The pharmaceutical company justifies its action with the fact that not all endpoints were evaluated within the scope of this non-prespecified data cut-off requested by the EMA. However, it is stated in the dossier submissions that the presentation of data cut-offs defined a priori as well as those required by regulatory authorities is necessary and that evaluations of the listed data cut-offs should be carried out and presented completely, i.e., for

all relevant endpoints collected. This also applies if a data cut-off was originally planned only for the evaluation of individual endpoints. In this context, it is particularly critical that it can be assumed that data on patient-reported endpoints will be added to the 2nd data cut-off to a significant extent. Patient-reported outcomes in the ASPEN study were observed until the end of treatment and, according to study records, 75% of subjects in the zanubrutinib arm and 68% of subjects in the ibrutinib arm were still under observation at the time of the 2nd data cut-off.

Furthermore, the evaluations submitted by the pharmaceutical company have been inadequately prepared. The pharmaceutical company submits a "constrained Longitudinal Data Analysis" (cLDA) for the evaluation of the EORTC QLQ-C30. For the "global health status" scale, evaluations are available on the basis of a mixed model for repeated measures (MMRM). The cLDA appears to be an end-of-treatment evaluation, with assessments apparently available for only 4 and 9 adults in the intervention and comparison arms, respectively, for the 1st data cut-off. From the figures presented on the course of studies, it can be concluded that assessments were only conducted for > 60% or > 50% of the subjects at the 1st data cut-off for cycle 19. The pharmaceutical company did not provide a breakdown of the return rates for the two data cut-offs. It remains unclear why the pharmaceutical company submits MMRM analyses exclusively for the global health status scale. Furthermore, for the "global health status" scale of the EORTC QLQ-C30, the pharmaceutical company descriptively reports how many subjects have "improved", "deteriorated" or remained "stable" at the end of treatment. No information is available on the basis of which criteria this categorisation is made. Therefore, the data presented cannot be meaningfully interpreted.

In addition, the pharmaceutical company does not provide any information on endpoint-specific durations of observation and on antineoplastic subsequent therapies in the dossier, which makes an adequate assessment of the study data even more difficult.

Overall, IQWiG states that, due to the incomplete data, an adequate weighing of the benefits and harms and thus an assessment of the additional benefit of zanubrutinib compared to the appropriate comparator therapy is not possible. A presentation of the usable study results contained in the dossier was also omitted.

After detailed consideration of IQWiG's discussion of the deficiencies in the dossier, the G-BA concurs with the IQWiG's assessment and, for its part, states that according to Chapter 5, Section 18, paragraph 1 of the Rules of Procedure of the G-BA, the preparation of the documents in the dossier deviates to an extent from the requirements specified in Chapter 5, Section 9 VerfO des G-BA, which is contrary to a proper assessment of the additional benefit.

In accordance with the regulation in Chapter 5, Section 18 of the Rules of Procedure of the G-BA, the benefit assessment examines whether there is evidence of an additional benefit for the medicinal product compared to the appropriate comparator therapy. The validity and completeness of the information in the dossier are also checked. The dossier template in Annex II must be used for compiling the documents. The data according to Chapter 5, Section

9, paragraphs 1, 4 to 8 of the Rules of Procedure of the G-BA must be prepared and submitted in accordance with the requirements specified in Modules 1 to 5. If the examination of the content of the dossier as part of the benefit assessment shows that the preparation of the documents for the proof of additional benefit does not meet the requirements specified in modules 1 to 5, in particular the requirements for the methodological presentation of the evidence in accordance with the principles of evidence-based medicine, because serious deficiencies can be identified in this respect, the G-BA can come to the conclusion that the evidence submitted is not sufficient to be able to derive statements on the additional benefit.

The preparation of the pharmaceutical company's data presented here does not comply with the requirements laid down in Chapter 5, Section 9 of the Regulation and proves to be inadequate and incomplete, so that it remains an obstacle to a proper assessment of the additional benefit.

Within the scope of the written statement, the pharmaceutical company submitted comprehensive evaluations of the study results of the 1st and 2nd data cut-offs subsequently. In this regard, IQWiG discussed at the oral hearing that the subsequently submitted data are very extensive, unstructured data that have not been prepared in accordance with Annex II to Chapter 5 of the Rules of Procedure and therefore do not represent a remedy for the incompleteness of the content. In particular, the pharmaceutical company still does not adequately consider the data on the patient-reported endpoints added at the 2nd data cut-off in the context of the subsequently submitted data. With its written statement, the pharmaceutical company submitted MMRM analysis on cycle 7 and on cycle 13. Although for cycle 19 the return rates at the 2nd data cut-off remain ≥ 70%, the pharmaceutical company does not include these data in the MMRM model. Thus, the point of criticism made by IQWiG in the benefit assessment regarding the non-inclusion of the additional data on patient-reported endpoints at the 2nd data cut-off has not been resolved.

The extensive amount of unstructured data also makes it difficult to check for completeness. In this respect, regardless of the fact that the pharmaceutical company has the right according to Chapter 5, Section 19, paragraphs 1 and 2 of the Rules of Procedure of the G-BA to comment on the benefit assessment of the medicinal product both in writing and orally upon publication of the benefit assessment on the website of the Federal Joint Committee and that the written and oral comments are included in the resolution on the adoption of the benefit assessment according to Section 92, paragraph 1, sentence 2, number 6 SGB V, it is the sole responsibility of the pharmaceutical company according to Section 5 paragraph 1 sentence 1 of the AM-NutzenV to prove in the dossier the additional benefit of the medicinal product with a new active ingredient. According to Section 5, paragraph 1, sentence 2 AM-NutzenV, the G-BA has no official duty to investigate.

The evaluations submitted with the written statement were therefore not suitable to enable a proper assessment of the additional benefit due to the inadequate processing. As a result, it must be concluded that the additional benefit according to Chapter 5, Section 18 paragraph 1, sentence 4 VerfO 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 Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first-line therapy for adults unsuitable for chemo-immunotherapy.

The G-BA determined a patient-individual therapy as an appropriate comparator therapy, taking into account the general condition and, if applicable, prior therapies and the duration of remission after initial therapy. In the context of patient-individual therapy, bendamustine + rituximab, bortezomib + dexamethasone + rituximab, ibrutinib, ibrutinib + rituximab, rituximab + cyclophosphamide + dexamethasone, bortezomib + rituximab and rituximab are considered suitable comparators.

The results of the open-label phase III ASPEN study (zanubrutinib versus ibrutinib) were presented for proof of additional benefit.

The preparation of the study data in the dossier proved to be seriously inadequate and incomplete in terms of content, which is an obstacle to a proper assessment of the additional benefit.

In the dossier, no complete evaluations of patient-reported endpoints collected in the study were available for either of the two available data cut-offs. In addition, complete subgroup analyses were lacking and there were deficiencies in the evaluation of the patient-reported endpoints presented.

The evaluations submitted with the written statement were also not suitable for a proper assessment of the additional benefit due to the inadequate processing.

As a result, it is therefore concluded that the additional benefit according to Chapter 5, Section 18 paragraph 1, sentence 4 VerfO is 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, subject to uncertainties.

The calculation of the pharmaceutical company is based on the patient numbers of the resolution on ibrutinib (resolution of 21 July 2016) and an assumed rate of increase based on the resolution on ibrutinib + rituximab (resolution of 20 February 2020).

The SHI routine data analysis on which the patient numbers from the 2016 ibrutinib procedure are based refers exclusively to subjects who received chemotherapy. Based on these data, it is therefore not possible to narrow down the subjects who are eligible for first-line therapy

with zanubrutinib. In addition, it can be assumed that the medical treatment situation in 2021 will deviate from the results of the routine data analysis with regard to the active ingredients used and their prescription frequency, for example due to the marketing authorisation of ibrutinib combination or monotherapy.

For the number of pretreated subjects, routine data analysis was also used to take into account those who had received chemotherapy in previous years, without restricting that the people actually need subsequent therapy due to relapse or refractoriness and are eligible for treatment with zanubrutinib. In addition, subjects with subsequent therapy in the year under review are already included in another percentage value. Overall, the approach tends to lead to overestimation.

Furthermore, the rate of increase used from the 2019 ibrutinib + rituximab study is subject to uncertainty. It cannot be ruled out that, based on current data from the Robert Koch Institute on the development of the overarching indication of non-Hodgkin lymphoma, a higher number of patients will result by 2021 compared to the procedure from 2016.

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: 5 April 2022):
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 Waldenström's macroglobulinaemia.

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: 1 June 2022).

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Zanubrutinib	1 x daily or 2 x daily	365	1	365

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Appropriate comparator therapy				
Patient-individual therapy taking into account the general condition and, if applicable, prior therapies and the duration of remission after initial therapy[a]				
Ibrutinib monotherapy				
Ibrutinib	1 x daily	365	1	365
Ibrutinib + rituximab				
Ibrutinib	1 x daily	365	1	365
Rituximab	Week 1 - 4: 1 x every 7 days Week 17 - 20: 1 x every 7 days	2	4	8

a The active ingredients or combinations of active ingredients bendamustine + rituximab, bortezomib + dexamethasone + rituximab, rituximab + cyclophosphamide + dexamethasone, bortezomib + rituximab and rituximab as monotherapy are suitable comparators for the present benefit assessment in the context of patient-individual therapy. However, these active ingredients or combinations of active ingredients are not approved in the present therapeutic indication, and therefore, no costs are presented for these active ingredients or combinations of active ingredients.

Consumption:

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 is patient-individual 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.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements were applied (average 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)[3]

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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Zanubrutinib	160 mg or 320 mg	320 mg	4 x 80 mg	365	1460 x 80 mg
Appropriate comparator therapy					
Patient-individual therapy taking into account the general condition and, if applicable, prior therapies and the duration of remission after initial therapy[a]					
Ibrutinib monotherapy					
Ibrutinib	420 mg	420 mg	1 x 420 mg	365	365 x 420 mg
Ibrutinib + rituximab					
Ibrutinib	420 mg	420 mg	1 x 420 mg	365	365 x 420 mg
Rituximab	375 mg/m² = 712.5 mg	712.5 mg	3 x 100 mg + 1 x 500 mg	8	24 x 100 mg + 8 x 500 mg

a The active ingredients or combinations of active ingredients bendamustine + rituximab, bortezomib + dexamethasone + rituximab, rituximab + cyclophosphamide + dexamethasone, bortezomib + rituximab and rituximab as monotherapy are suitable comparators for the present benefit assessment in the context of patient-individual therapy. However, these active ingredients or combinations of active ingredients are not approved in the present therapeutic indication, and therefore, no costs are presented for these active ingredients or combinations of active ingredients.

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

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					

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
Zanubrutinib 80 mg	120 HC	€ 6,563.80	€ 1.77	€ 371.57	€ 6,190.46
Appropriate comparator therapy					
Ibrutinib 420 mg	28 FCT	€ 5,852.87	€ 1.77	€ 0.00	€ 5,851.10
Rituximab 500 mg	1 CIS	€ 1,777.30	€ 1.77	€ 84.18	€ 1,691.35
Rituximab 100 mg	2 CIS	€ 717.18	€ 1.77	€ 33.50	€ 681.91
Abbreviations: FCT = film-coated tablets; HC = hard capsules; CIS = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 1 June 2022

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 zanubrutinib. These examinations are also required when using ibrutinib and rituximab as an appropriate comparator therapy. Since there is no regular difference between the medicinal product to be assessed and the appropriate comparator therapy with regard to the tests for hepatitis B, the costs for additionally required SHI services for tests for hepatitis B are not 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 to 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, additional required SHI services are incurred that usually differ between the medicinal product to be assessed and rituximab (in combination with ibrutinib) as an appropriate comparator therapy and are consequently taken into account as additional required SHI services in the resolution.

Designation of the therapy	Designation of the service	Treatment days per patient per year	Costs per pack or service	Costs per patient per year
Medicinal product to be assessed: Zanubrutinib Appropriate comparator therapy ibrutinib (monotherapy), ibrutinib + rituximab				
Rituximab	*Premedication* Antihistamines e.g., dimetindene IV 1 mg/ 10 kg = 7.7 mg Antipyretics e.g. paracetamol oral 1,000 mg	 8 8	 € 15.19[4] € 1.36[5]	 € 60.76 € 1.36

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 € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

4 after deduction of the statutory rebates according to Sections 130 and 130a SGB V

5 calculated from the pharmacy sales price of € 1.50 minus € 0.08 (deduction according to Section 130 SGB V) and € 0.06 (deduction according to Section 130 a SB V).

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 26 January 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 14 December 2021, 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 1, sentence 2 VerfO.

By letter dated 15 December 2021 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 11 March 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 15 March 2022. The deadline for submitting written statements was 5 April 2022.

The oral hearing was held on 25 April 2022.

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 8 June 2022, and the proposed resolution was approved.

At its session on 16 June 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	26 January 2021	Determination of the appropriate comparator therapy

Working group Section 35a	21 April 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	25 April 2022	Conduct of the oral hearing
Working group Section 35a	04.05.2022; 18.05.2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	8 June 2022	Concluding discussion of the draft resolution
Plenum	16 June 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 June 2022

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

Prof. Hecken