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: chronic lymphocytic leukemia (CLL), relapsed/refractory)

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 15 November 2022, BeiGene Germany GmbH received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2a, letter a to Regulation (EC) No. 1234/2008 of the commission of 24 November 2008 concerning the examination of amendments 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 chronic lymphocytic leukemia (CLL) 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 chronic lymphocytic leukemia (CLL).

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

Brukinsa as monotherapy is indicated for the treatment of adult patients with relapsed/refractory chronic lymphocytic leukemia (CLL).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) who have neither received a BTK inhibitor nor a BCL2 inhibitor

Appropriate comparator therapy for zanubrutinib:

- Ibrutinib

or

- Venetoclax + rituximab

or

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

- a chemoimmunotherapy with FCR or BR or ClbR (in each case only if there is a long relapse-free interval and no genetic risk factors)

b) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BTK inhibitor

Appropriate comparator therapy for zanubrutinib:
- Venetoclax + rituximab

c) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BCL2 inhibitor

Appropriate comparator therapy for zanubrutinib:
- Ibrutinib

d) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BTK inhibitor and a BCL2 inhibitor

Appropriate comparator therapy for zanubrutinib:
- Patient-individual therapy with selection of:
  - idelalisib in combination with rituximab,
  - bendamustine in combination with rituximab,
  - chlorambucil in combination with rituximab and
  - best supportive care;

  taking into account comorbidities, general condition, genetic risk factors as well as success and tolerability of prior therapy

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, according to the authorisation status, the cytostatic agents chlorambucil, cyclophosphamide and fludarabine; the B-cell receptor inhibitors acalabrutinib, duvelisib, ibrutinib and idelalisib; the BCL-2 inhibitor venetoclax; the PI3K inhibitor duvelisib; the anti-CD-20 antibody rituximab and the glucocorticoids prednisolone, prednisone and dexamethasone are available for the treatment of relapsed/ refractory chronic lymphocytic leukemia. The chronic lymphocytic leukemia is a type of non-Hodgkin lymphoma. Accordingly, the active ingredients bendamustine, cytarabine, doxorubicin, etoposide, mitoxantrone, trofosfamide, vinblastine and vincristine also have a marketing authorisation for the present therapeutic indication. Some of the marketing authorisations are tied to specific concomitant active ingredients.

on 2. In the present therapeutic indication, allogeneic stem cell transplantation represents a non-medicinal treatment option. However, the G-BA expects for the present treatment setting that allogeneic stem cell transplantation is not indicated at the time of therapy, or eligible only in individual cases for a few patients and is therefore not included among the standard therapies in the therapeutic indication.

on 3. For the present therapeutic indication, the resolutions of the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V on the following active ingredients are available:

- Acalabrutinib (resolution of 5 August 2021)
- Duvelisib (resolution of 21.07.2022)
- Ibrutinib (resolutions of 16 March 2017 and 21 July 2016)
- Idelalisib (resolutions of 16 March 2017 and 15 September 2016)
- Venetoclax (resolution of 16 May 2019)

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

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

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

For the present therapeutic indication, it is presumed that the patients are in need of treatment (for example, stage C Binet). Furthermore, for the present therapeutic indication, it is assumed that an allogeneic stem cell transplantation is not indicated at the time of therapy.

On the basis of the available evidence, the G-BA considers it appropriate to divide the patients into different patient populations for the appropriate comparator therapy according to the therapeutic indication with relapsed/ refractory chronic lymphocytic leukemia (CLL), wherein these patient populations are differentiated depending on the prior therapy/ therapies - specifically with a BTK inhibitor and/or BCL2 inhibitor:

a) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) who have neither received a BTK inhibitor nor a BCL2 inhibitor

If patients have not previously received either a BTK or a BCL2 inhibitor, several treatment options come into question according to the available evidence. The combination therapy of venetoclax + rituximab and therapy with a BTK inhibitor are mentioned as particularly effective treatment options by guidelines and in the written statement of the scientific-medical society.

By resolution of 16 May 2019, the G-BA identified an indication of a minor additional benefit of venetoclax + rituximab compared to BR for patients without a 17p deletion and/or TP53 mutation who have received at least one prior therapy and for whom bendamustine in combination with rituximab (BR) is the appropriate patient-individual therapy.

By resolution of 21 July 2016, the G-BA identified a hint of a non-quantifiable additional benefit of ibrutinib in the benefit assessment over ofatumumab for the patient population for whom chemotherapy is not indicated.

In both the benefit assessment for venetoclax + rituximab and for ibrutinib monotherapy, no data were available for other patient groups that relate to the present patient population. Based on the clear recommendation in guidelines as well as the written statement of the scientific-medical society, both ibrutinib and venetoclax + rituximab are determined as comparator therapies for the entire patient population a) for patients who have not yet received a BTK inhibitor and/or BCL2 inhibitor. No preference can be derived for one of the two treatment options, so that they are considered to be equally appropriate treatment options.

Acalabrutinib is another approved BTK inhibitor. By resolution of 5 August 2021, the G-BA identified a hint for a considerable additional benefit over idelalisib in combination with rituximab for the group of patients following prior therapy who have a 17p deletion or TP53 mutation or for whom chemoimmunotherapy is not indicated for other reasons.

For patients with CLL after prior therapy who do not have a 17p deletion or TP53 mutation and for whom chemoimmunotherapy is indicated, the additional benefit was assessed as being unproven. For the patient group for whom bendamustine in combination with rituximab represents the patient-individual appropriate therapy, neither an advantage nor a disadvantage could be determined for overall survival, the

endpoints of the category morbidity, health-related quality of life and side effects overall. No usable data were available for patients for whom a therapy other than bendamustine in combination with rituximab is the appropriate patient-individual therapy.

Overall, there is no uniform assessment for the patient group after prior therapy.

The clinical significance of acalabrutinib cannot be conclusively assessed at present. Acalabrutinib is not determined to be an appropriate comparator therapy for the present resolution.

In addition, according to guideline recommendations and the written statement of the scientific-medical society, a repetition of the primary therapy (fludarabine + cyclophosphamide + rituximab (FCR), bendamustine + rituximab (BR), chlorambucil + rituximab (ClbR)) can also be considered for patients who show a late relapse after chemoimmunotherapy. It must be taken into account that chemoimmunotherapy is only indicated if the patients do not have any genetic risk factors. According to the current state of medical knowledge, the presence of a 17p deletion/ TP53 mutation and an unmutated IGHV status are considered genetic risk factors.

b) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BTK inhibitor

The present guidelines do not explicitly recommend the use of venetoclax + rituximab after the use of a BTK inhibitor. However, as stated in patient population a), there is a clear recommendation for the use of venetoclax + rituximab in patients with r/r CLL. According to the written statement of the German Society for Haematology and Medical Oncology (DGHO), the combination venetoclax + rituximab is the standard therapy for patients with r/r CLL. According to DGHO e.V. (German Society for Haematology and Medical Oncology), a repetition of therapy with a BTK inhibitor does not appear to make much sense against the background of the occurrence of specific resistance mutations.

As stated for patient population a), by resolution of 16 May 2019, the G-BA determined a indication of a minor additional benefit of venetoclax + rituximab compared with BR for patients without a 17p deletion and/or TP53 mutation who have received at least one prior therapy and for whom bendamustine in combination with rituximab (BR) is the appropriate patient-individual therapy. No data were available for the other patient populations.

It is assumed that for patients who have already been treated with a BTK inhibitor but have not yet received therapy with venetoclax + rituximab, repeating chemoimmunotherapy is not a primary consideration.

c) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BCL2 inhibitor

The guidelines do not explicitly recommend the use of ibrutinib after the use of a BCL2 inhibitor. However, as stated in patient population a), BTK inhibitors are considered a

particularly effective therapeutic alternative for r/r CLL. The critical comments of the DGHO on a possible re-treatment due to specific resistance mechanisms, as explained under patient population b), apply vice versa to a prior therapy with a BCL2 inhibitor.

As stated for patient population a), by resolution of 21 July 2016, the G-BA identified in the benefit assessment of ibrutinib a hint for a non-quantifiable additional benefit over ofatumumab + BSC for the patient population for whom chemotherapy is not indicated. No data were available for other patient populations.

It is assumed that for patients who have already been treated with a BCL2 inhibitor but have not yet received therapy with a BTK inhibitor, repeating chemoimmunotherapy is not a primary consideration.

Analogous to the comments on patient population a), acalabrutinib is another approved BTK inhibitor. By resolution of 5 August 2021, the G-BA identified a hint for a considerable additional benefit over idelalisib in combination with rituximab for the group of patients following prior therapy who have a 17p deletion or TP53 mutation or for whom chemoimmunotherapy is not indicated for other reasons.

For patients with CLL after prior therapy who do not have a 17p deletion or TP53 mutation and for whom chemoimmunotherapy is indicated, the additional benefit was assessed as being unproven. For the patient group for whom bendamustine in combination with rituximab represents the patient-individual appropriate therapy, neither an advantage nor a disadvantage could be determined for overall survival, the endpoints of the category morbidity, health-related quality of life and side effects overall. No usable data were available for patients for whom a therapy other than bendamustine in combination with rituximab is the appropriate patient-individual therapy.

Overall, there is no uniform assessment for the patient group after prior therapy.

The clinical significance of acalabrutinib cannot be conclusively assessed at present. Acalabrutinib is not determined to be an appropriate comparator therapy for the present resolution.

d) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BTK inhibitor and one BCL2 inhibitor

The therapy of these patients is characterised by patient-individual treatment decisions. The treatment strategy depends in particular on the genetic risk factors on the one hand and on comorbidities, general condition, success and tolerability of the prior therapy on the other.

Taking into account the comments on the development of resistance mechanisms, patients with r/r CLL who have already received both a BTK inhibitor and a BCL2 inhibitor should not primarily be considered for re-treatment with them.

According to the available guidelines and the DGHO, the approved treatment option for this patient population is idelalisib in combination with rituximab. In the benefit assessment of idelalisib in combination with rituximab, an additional benefit was not

proven due to lack of data in all patient groups (resolutions of 21 July 2016 and 15 September 2016). In the context of patient-individual therapy, the G-BA nevertheless considers idelalisib + rituximab to be a suitable comparator due to the limited treatment options and the recommendations of the guidelines.

Furthermore, according to the guidelines, the chemoimmunotherapies bendamustine + rituximab and chlorambucil + rituximab can be considered as approved treatment options. Patients with genetic risk factors show a poor response to chemoimmunotherapies, which is why chemoimmunotherapy is not a regular therapeutic alternative for these patients. According to the current state of medical knowledge, the presence of a 17p deletion/ TP53 mutation are considered genetic risk factors.

Due to the advanced treatment setting, the G-BA assumes a shift from CLL-specific therapy to best supportive care for a relevant percentage of patients, especially those with a poor general condition. Best supportive care is defined as the therapy that provides the best possible, patient-individual, optimised supportive treatment to alleviate symptoms and improve quality of life. Best supportive care is only considered for patients with low life expectancy and very poor general condition.

Another approved therapeutic alternative is the PI3K inhibitor duvelisib. This active ingredient is currently not being sold. Duvelisib is therefore not considered as an appropriate comparator therapy.

Overall, the G-BA thus determines the appropriate comparator therapy to be a patient-individual therapy for patients with prior therapy with at least one BTK inhibitor and one BCL2 inhibitor, selecting idelalisib + rituximab, bendamustine + rituximab, chlorambucil + rituximab and best supportive care, taking into account comorbidities, general condition, genetic risk factors as well as success and tolerability to the prior therapy.

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:

a) <u>Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) who have neither received a BTK inhibitor nor a BCL2 inhibitor</u>

Indication of a minor additional benefit.

Justification:

For the proof of an additional benefit of zanubrutinib, the pharmaceutical company submits the still ongoing, open-label, randomised, controlled phase III ALPINE study for the

comparison of zanubrutinib versus ibrutinib. The study has been conducted in 117 study sites across Asia-Pacific, Australia, Europe and North America since 2018.

The study enrolled adult patients with relapsed and/or refractory CLL or small cell lymphocytic lymphoma (SLL) who were pretreated with at least 1 systemic therapy. Prior treatment with a BTK inhibitor was not allowed. The majority of patients were pretreated with a therapy (approx. 58%). The majority of the prior therapies were chemoimmunotherapies (approx. 78%). Patients had to have a need for treatment according to the criteria of the International Workshop on Chronic Lymphocytic Leukemia (iwCLL), a general condition according to Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of 0 to 2 and a life expectancy > 6 months.

The total of 652 patients were stratified by age (< 65 years vs ≥ 65 years), geographic region (China vs non-China), refractoriness (yes vs no), and 17p deletion/ TP53 mutational status (yes vs no) - were randomised in a 1:1 ratio into the 2 study arms (zanubrutinib N = 327, ibrutinib N = 325).

Treatment with zanubrutinib or ibrutinib was continuous in each case according to the product information until disease progression, the occurrence of unacceptable toxicity, discontinuation of therapy or discontinuation of participation in the study by the patient or the doctor.

In addition to the overall response rate as the primary endpoint, overall survival, morbidity, health-related quality of life and adverse events (AEs) were collected as patient-relevant secondary endpoints.

For the ALPINE study, 3 pre-specified data cut-offs are available:

- 1st data cut-off (31.12.2020): 12 months after randomisation of about 415 patients.
- 2nd data cut-off (01.12.2021): 12 months after randomisation of about 600 patients.
- 3rd data cut-off (08.08.2022): Event-controlled analysis after the occurrence of 205 events for progression-free survival (final data cut-off).

The analyses submitted by the pharmaceutical company for the final data cut-off of 08.08.2022 are used for the benefit assessment.

Extent and probability of the additional benefit

Mortality

Overall survival

The endpoint of overall survival was defined in the ALPINE study as the time from the start of study treatment to death from any cause. There is no statistically significant difference between the treatment arms here.

With regard to overall survival, an additional benefit of zanubrutinib compared to ibrutinib is therefore not proven.

For the endpoint, there is an effect modification due to the age characteristic. For patients < 65 years of age, there is a statistically significant difference to the advantage of zanubrutinib.

In contrast, for patients ≥ 65 years of age, there is no statistically significant difference between the treatment arms.

This effect modification is not evident in other endpoints. Overall, the significance of the available subgroup results is considered insufficient for the assessment of the additional benefit.

Morbidity

Progression-free survival (PFS)

Progression-free survival (PFS) is defined in the study as the time from the start of study treatment until the first documented disease progression or death, whichever occurred first. For the PFS, there is a statistically significant difference to the advantage of zanubrutinib compared to ibrutinib.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component of mortality is already assessed via the endpoint of overall survival as an independent endpoint. The morbidity component is assessed according to iwCLL criteria and thus, predominantly by means of laboratory parametric, imaging and haematological procedures.

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

Symptomatology (EORTC QLQ-C30)

The symptomatology of the ALPINE study patients is assessed using the symptom scales of the EORTC QLQ-C30 questionnaire.

For the endpoints of fatigue, nausea and vomiting, pain, appetite loss, dyspnoea, insomnia and constipation, there was no statistically significant difference between the treatment arms.

Solely for the endpoint of diarrhoea, there is a statistically significant difference between the treatment arms to the advantage of zanubrutinib.

Health status (EQ-5D VAS)

For the endpoint of health status, assessed by EQ-5D VAS, there is no statistically significant difference between the treatment arms.

In the overall analysis of the results, neither an advantage nor a disadvantage is found with regard to morbidity.

Health-related quality of life

The quality of life of the ALPINE study patients is assessed using the functional scales of the EORTC QLQ-C30 questionnaire.

There is no statistically significant difference between the treatment arms for the endpoints of general health status, physical functioning, role functioning, cognitive functioning, emotional functioning and social functioning.

With regard to health-related quality of life, there is no statistically significant difference between the treatment arms.

Side effects

Adverse events in total

In the ALPINE study, AEs occurred in both treatment arms in almost all study participants. The results were only presented additionally.

Serious AEs (SAEs) and discontinuation due to AEs

For the endpoints of SAEs and discontinuation due to AEs, there is a statistically significant difference to the advantage of zanubrutinib compared to ibrutinib.

Severe AEs

For the endpoint of severe AEs, there is no statistically significant difference between the treatment arms.

Specific AEs

Cardiac disorders (severe AE)

For the endpoint of cardiac disorders (severe AE), there is a statistically significant difference to the advantage of zanubrutinib compared to ibrutinib.

Muscle spasms (AE)

For the endpoint of muscle spasms (AE), there is a statistically significant difference to the advantage of zanubrutinib compared to ibrutinib.

Infections and infestations (severe AE) and bleeding (AE)

For the endpoints of infections and infestations (severe AE) and bleeding (AE), there is no statistically significant difference between the treatment arms.

In summary, advantages of treatment with zanubrutinib can be identified due to positive effects in SAEs and discontinuations due to AEs, and in detail, for specific AEs. Overall, this is assessed as a relevant improvement in side effects.

Overall assessment/ conclusion

The present benefit assessment of zanubrutinib as monotherapy for the treatment of adults with relapsed/refractory chronic lymphocytic leukemia (CLL) who have received neither a BTK inhibitor nor a BCL2 inhibitor is based on the results of the ALPINE study on the endpoint categories of mortality, morbidity, health-related quality of life and side effects compared to ibrutinib.

For the endpoint of overall survival, no statistically significant difference was detected between the treatment arms.

There are no relevant advantages or disadvantages for the endpoint categories of morbidity assessed using the symptom scales of the EORTC QLQ-C30 questionnaire and the EQ 5D VAS

as well as for the endpoint category of health-related quality of life assessed using the functional scales of the EORTC QLQ-C30 questionnaire.

In terms of side effects, there are positive effects of zanubrutinib compared to ibrutinib for the endpoints of SAE, discontinuation due to AEs, and in detail, for the specific AEs. The extent of the advantage is assessed as low overall.

In the overall assessment, zanubrutinib as monotherapy for the treatment of adults with relapsed/refractory chronic lymphocytic leukemia (CLL) who have received neither a BTK inhibitor nor a BCL2 inhibitor is therefore found to have a minor additional benefit compared with ibrutinib.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the open-label, randomised, phase III ALPINE study.

The risk of bias at study level is rated as low for the endpoint of overall survival.

For the results of the endpoints of the endpoint categories of morbidity and health-related quality of life, the risk of bias is rated as high in each case. The open-label study design leads to a high risk of bias for the endpoints that cannot be assigned to SAEs or severe AEs.

Uncertainties arise with regard to the adequate representation of the German health care context in the ALPINE study, since a high percentage of patients received chemoimmunotherapy in the prior therapy, and at the same time the percentage of patients with high-risk genetics was not stated at the start of the study.

However, these uncertainties are not rated so high as to justify a downgrading of the reliability of data of the overall assessment. Thus, the reliability of data for the additional benefit determined is classified in the category "indication".

b) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BTK inhibitor

An additional benefit is not proven.

Justification:

For adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BTK inhibitor, the pharmaceutical company does not submit any data for the assessment of additional benefit. Therefore, an additional benefit is not proven.

c) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BCL2 inhibitor

An additional benefit is not proven.

Justification:

For adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BCL2 inhibitor, the pharmaceutical company presents the ALPINE study. The study enrolled a small number of patients with relapsed/ refractory CLL after prior therapy with at least one BCL2 inhibitor (zanubrutinib N = 7, ibrutinib N = 8). The pharmaceutical company does not submit separate evaluations for this small sub-population. The ALPINE study is not relevant for the benefit assessment of patients with relapsed/ refractory CLL after prior therapy with at least one BCL2 inhibitor.

Thus, there are no suitable data for the assessment of the additional benefit of zanubrutinib compared with the appropriate comparator therapy. Therefore, an additional benefit is not proven.

d) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BTK inhibitor and a BCL2 inhibitor

An additional benefit is not proven.

Justification:

For adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BTK inhibitor and one BCL2 inhibitor, the pharmaceutical company does not submit any data for the assessment of additional benefit. Therefore, an additional benefit is not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the medicinal product "Brukinsa" with the active ingredient zanubrutinib. The therapeutic indication assessed here is the treatment of adult patients with relapsed/refractory chronic lymphocytic leukemia (CLL). In the therapeutic indication under consideration, four patient groups were distinguished and the appropriate comparator therapy was determined as follows:

a) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) who have neither received a BTK inhibitor nor a BCL2 inhibitor

The appropriate comparator therapy includes monotherapy with ibrutinib and combination therapy with venetoclax and rituximab, or chemoimmunotherapy with FCR or BR or ClbR only in the case of a long relapse-free interval and the absence of genetic risk factors.

and

b) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BTK inhibitor

The appropriate comparator therapy comprises the combination therapy of venetoclax and rituximab.

and

c) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BCL2 inhibitor

The appropriate comparator therapy includes monotherapy with ibrutinib

and

d) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BTK inhibitor and a BCL2 inhibitor

The appropriate comparator therapy includes both the combination therapy of idelalisib and rituximab, bendamustine and rituximab, chlorambucil and rituximab, as well as best supportive care, which are available for a patient-individual treatment decision, taking into account comorbidities, general condition, genetic risk factors, and success and tolerability of the prior therapy.

About patient group a)

The pharmaceutical company presents data from the ALPINE study comparing zanubrutinib versus ibrutinib.

For the endpoint of overall survival, no statistically significant difference was detected between the treatment arms.

For the endpoint categories of morbidity and health-related quality of life assessed using the symptom scales or the functional scales of the EORTC QLQ-C30 questionnaire as well as the EQ 5D VAS, there were also no advantages or disadvantages.

In terms of side effects, there are positive effects of zanubrutinib compared to ibrutinib for the endpoints of SAE, discontinuation due to AEs, and in detail, for the specific AEs. The extent of the advantage is assessed as low overall.

The data basis is subject to some uncertainties, which, however, are not rated to be so high as to justify a downgrading of the reliability of data.

In the overall assessment, an indication of a minor additional benefit compared to ibrutinib is identified.

About patient groups b) to d)

No data are available to allow an assessment of the additional benefit. An additional benefit 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 information from the dossier of the pharmaceutical company. This information is subject to uncertainties in individual calculation steps.

When determining the number of patients with CLL, there are discrepancies between the data sources used. In addition, the identification of subjects who received at least one prescription of CLL-specific active ingredients in 2020 does not take into account those patients who in spite of needing treatment in 2020 are not receiving specific therapy but, for example, best supportive care and are eligible for zanubrutinib. This applies in particular to patients after prior therapy with at least one BTK inhibitor and one BCL2 inhibitor. In addition, an unknown number of patients, who received a change of therapy in the form of a repetition of the initial therapy or before the period of 8 years used in the routine data analysis, is excluded. These are also to be included in the target population.

Due to the more suitable and up-to-date data basis, the range shown here for the SHI target population represents a better approximation to the expected number of patients in the SHI target population than the previous number in previous procedures.

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: 10 February 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 chronic lymphocytic leukemia.

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).

The publications by Robak et al., Fischer K. et al., Goede, V., et al. and Furman et al. were used for the cost representation of fludarabine and cyclophosphamide in combination with rituximab or bendamustine in combination with rituximab or chlorambucil in combination with rituximab or idelalisib in combination with rituximab against the background of the missing information on the dosage of the respective combination therapy in the respective product information. The information on the duration of treatment (6 cycles) is based on the information in the rituximab product information. According to the rituximab product information, it is administered in combination with chemotherapy for a total of 6 cycles. In contrast, the information for idelalisib in combination with rituximab of 8 cycles is also based on Furmann et al.

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 the maximum treatment duration, if specified in the product information.

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	365.0	1	365.0
	or			
	Continuously, 2 x daily	365.0	1	365.0
Appropriate comparator therapy				
a) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) who have neither received a BTK inhibitor nor a BCL2 inhibitor				
Ibrutinib monotherapy				
Ibrutinib	Continuously, 1 x daily	365.0	1	365.0
Venetoclax + rituximab				
Venetoclax	Continuously, 1 x daily	365.0	1	365.0
Rituximab	Day 1 of a 28-day cycle	6.0	1	6.0
Chemoimmunotherapy with FCR or BR or ClbR (in each case only if there is a long recurrence-free interval and no genetic risk factors)				
Fludarabine +cyclophosphamide + rituximab (FCR)[2]				
Fludarabine	Day 1, 2 and 3 of a 28-day cycle	6.0	3	18.0
Cyclophosphamide	Day 1, 2 and 3 of a 28-day cycle	6.0	3	18.0
Rituximab	Day 1 of a 28-day cycle	6.0	1	6.0
Bendamustine + rituximab (BR)[3]				
Bendamustine	Day 1 and 2 of a 28-day cycle	6.0	2	12.0

[2] Robak T, et al., Rituximab Plus Fludarabine and Cyclophosphamide Prolongs Progression-Free Survival Compared With Fludarabine and Cyclophosphamide Alone in Previously Treated Chronic Lymphocytic Leukemia. J Clin Oncol 28:1756-1765

[3] Fischer K, et al., Bendamustine Combined With Rituximab in Patients With Relapsed and/or Refractory Chronic Lymphocytic Leukemia: A Multicentre Phase II Trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 29:3559-3566.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Rituximab	Day 1 of a 28-day cycle	6.0	1	6.0
Chlorambucil + rituximab (ClbR)[4]				
Chlorambucil	Day 1 and 15 of a 28-day cycle	6.0	2	12.0
Rituximab	Day 1 of a 28-day cycle	6.0	1	6.0
b) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BTK inhibitor				
Venetoclax + rituximab				
Venetoclax	Continuously, 1 x daily	365.0	1	365.0
Rituximab	Day 1 of a 28-day cycle	6.0	1	6.0
c) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BCL2 inhibitor				
Ibrutinib monotherapy				
Ibrutinib	Continuously, 1 x daily	365.0	1	365.0
d) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BTK inhibitor and a BCL2 inhibitor				
Idelalisib in combination with rituximab[5]				
Idelalisib	Continuously, 2 x daily	365.0	1	365.0
Rituximab	Once on week 1, 2, 4, 6, 8, 12, 16 and 20	8.0	1	8.0
Bendamustine in combination with rituximab (BR)[4]				
Bendamustine	Day 1 and 2 of a 28-day cycle	6.0	2	12.0
Rituximab	Day 1 of a 28-day cycle	6.0	1	6.0

[4] Goede, V., et al., Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med, 2014. 370(12): p. 1101-10

[5] Furman, R., et al, Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia. N Engl J Med 2014;370 (11): p. 997-1007

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Chlorambucil in combination with rituximab[5]				
Chlorambucil	Day 1 and 15 of a 28-day cycle	6.0	2	12.0
Rituximab	Day 1 of a 28-day cycle	6.0	1	6.0
Best supportive care				
Best supportive care[6]	Different from patient to patient			

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)[7].

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.

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

[6] In the case of a comparison with best supportive care, also to be used additionally for the medicinal product to be assessed.
[7] 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	320 mg	320 mg	4 x 80 mg	365.0	1460 x 80 mg
	or				
	160 mg	320 mg	4 x 80 mg	365.0	1460 x 80 mg
Appropriate comparator therapy					
a) Adults with relapsed/refractory chronic lymphocytic leukemia (CLL) who have not yet received a BTK inhibitor and/or BCL2 inhibitor					
Ibrutinib monotherapy					
Ibrutinib	420 mg	420 mg	1 x 420 mg	365.0	365 x 420 mg
Venetoclax + rituximab					
Venetoclax	Week 1: 20 mg Week 2: 50 mg Week 3: 100 mg Week 4: 200 mg Week 5 et seqq.: 400 mg	Week 1: 20 mg Week 2: 50 mg Week 3: 100 mg Week 4: 200 mg Week 5 et seqq.: 400 mg	Week 1: 2 x 10 mg Week 2: 1 x 50 mg Week 3: 1 x 100 mg Week 4: 2 x 100 mg Week 5 et seqq.: 4 x 100 mg	365.0	14 x 10 mg + 7 x 50 mg + 1,369 x 100 mg
Rituximab	Cycle 1: 375 mg/m^2 = 712.5 mg Cycle 2 - 6: 500 mg/m^2 = 950 mg	Cycle 1: 712.5 mg Cycle 2 - 6: 950 mg	Cycle 1: 3 x 100 mg + 1 x 500 mg Cycle 2 - 6: 2 x 500 mg	6.0	3 x 100 mg + 11 x 500 mg

Chemoimmunotherapy with FCR or BR or ClbR (in each case only if there is a long recurrence-free interval and no genetic risk factors)

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Fludarabine + cyclophosphamide + rituximab (FCR)					
Fludarabine	25 mg/m²	47.5 mg	1 x 50 mg	18	18 x 50 mg
Cyclo-phosphamide	250 mg/m²	475 mg	1 x 500 mg	18	18 x 500 mg
Rituximab	Cycle 1: 375 mg/m² = 712.5 mg Cycle 2 - 6: 500 mg/m² = 950 mg	Cycle 1: 712.5 mg Cycle 2 - 6: 950 mg	Cycle 1: 3 x 100 mg + 1 x 500 mg Cycle 2 - 6: 2 x 500 mg	6.0	3 x 100 mg + 11 x 500 mg
Bendamustine + rituximab (BR)					
Bendamustine	90 mg/m² = 171 mg	171 mg	1 x 100 mg + 3 x 25 mg	12.0	12 x 100 mg + 36 x 25 mg
Rituximab	Cycle 1: 375 mg/m² = 712.5 mg Cycle 2 - 6: 500 mg/m² = 950 mg	Cycle 1: 712.5 mg Cycle 2 - 6: 950 mg	Cycle 1: 3 x 100 mg + 1 x 500 mg Cycle 2 - 6: 2 x 500 mg	6.0	3 x 100 mg + 11 x 500 mg
Chlorambucil + rituximab (ClbR)					
Chlorambucil	0.5 mg/kg = 38.5 mg	38.5 mg	19 x 2 mg	12.0	228 x 2 mg
Rituximab	Cycle 1: 375 mg/m² = 712.5 mg	Cycle 1: 712.5 mg	Cycle 1: 3 x 100 mg + 1 x 500 mg	6.0	3 x 100 mg + 11 x 500 mg
	Cycle 2 - 6: 500 mg/m² = 950 mg	Cycle 2 - 6: 950 mg	Cycle 2 - 6: 2 x 500 mg		
b) Adults with relapsed/ refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BTK inhibitor					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Venetoclax + rituximab					
Venetoclax	Week 1: 20 mg Week 2: 50 mg Week 3: 100 mg Week 4: 200 mg Week 5 et seqq.: 400 mg	Week 1: 20 mg Week 2: 50 mg Week 3: 100 mg Week 4: 200 mg Week 5 et seqq.: 400 mg	Week 1: 2 x 10 mg Week 2: 1 x 50 mg Week 3: 1 x 100 mg Week 4: 2 x 100 mg Week 5 et seqq.: 4 x 100 mg	365.0	14 x 10 mg + 7 x 50 mg + 1,369 x 100 mg
Rituximab	Cycle 1: 375 mg/m^2 = 712.5 mg	Cycle 1: 712.5 mg	Cycle 1: 3 x 100 mg + 1 x 500 mg	6.0	3 x 100 mg + 11 x 500 mg
	Cycle 2 - 6: 500 mg/m^2 = 950 mg	Cycle 2 - 6: 950 mg	Cycle 2 - 6: 2 x 500 mg		
c) Adults with relapsed/ refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BCL2 inhibitor					
Ibrutinib monotherapy					
Ibrutinib	420 mg	420 mg	1 x 420 mg	365.0	365 x 420 mg
d) Adults with relapsed/ refractory chronic lymphocytic leukemia (CLL) after prior therapy with at least one BTK inhibitor and a BCL2 inhibitor					
idelalisib in combination with rituximab					
Idelalisib	150 mg	300 mg	2 x 150 mg	365.0	730 x 150 mg
Rituximab	Cycle 1: 375 mg/m^2 = 712.5 mg Cycle 2 - 8: 500 mg/m^2 = 950 mg	Cycle 1: 712.5 mg Cycle 2 - 8: 950 mg	Cycle 1: 3 x 100 mg + 1 x 500 mg Cycle 2 - 8: 2 x 500 mg	8.0	3 x 100 mg + 15 x 500 mg
Bendamustine in combination with rituximab					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Bendamustine	90 mg/m² = 171 mg	171 mg	1 x 100 mg + 3 x 25 mg	12.0	12 x 100 mg + 36 x 25 mg
Rituximab	Cycle 1: 375 mg/m² = 712.5 mg	Cycle 1: 712.5 mg	Cycle 1: 3 x 100 mg + 1 x 500 mg	6.0	3 x 100 mg + 11 x 500 mg
	Cycle 2 - 6: 500 mg/m² = 950 mg	Cycle 2 - 6: 950 mg	Cycle 2 - 6: 2 x 500 mg		
Chlorambucil in combination with rituximab					
Chlorambucil	0.5 mg/kg = 38.5 mg	38.5 mg	19 x 2 mg	12.0	228 x 2 mg
Rituximab	Cycle 1: 375 mg/m² = 712.5 mg	Cycle 1: 712.5 mg	Cycle 1: 3 x 100 mg + 1 x 500 mg	6.0	3 x 100 mg + 11 x 500 mg
	Cycle 2 - 6: 500 mg/m² = 950 mg	Cycle 2 - 6: 950 mg	Cycle 2 - 6: 2 x 500 mg		
Best supportive care					
Best supportive care	Different from patient to patient				

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					
Zanubrutinib	120 HC	€ 5,995.07	€ 2.00	€ 581.30	€ 5,411.77
Appropriate comparator therapy					
Bendamustine 100 mg	1 PIC	€ 331.00	€ 2.00	€ 40.46	€ 288.54
Bendamustine 100 mg	5 PIC	€ 1,620.92	€ 2.00	€ 204.07	€ 1,414.85
Bendamustine 25 mg	1 PIC	€ 99.35	€ 2.00	€ 11.15	€ 86.20
Bendamustine 25 mg	5 PIC	€ 414.39	€ 2.00	€ 51.01	€ 361.38
Best supportive care	Different from patient to patient				
Chlorambucil 2 mg	50 FCT	€ 37.73	€ 2.00	€ 2.51	€ 33.22
Cyclophosphamide 500 mg	6 PSI	€ 84.41	€ 2.00	€ 9.25	€ 73.16
Fludarabine 50 mg	1 CIS	€ 118.50	€ 2.00	€ 5.09	€ 111.41
Fludarabine 50 mg	5 DSS	€ 546.82	€ 2.00	€ 25.41	€ 519.41
Ibrutinib 420 mg	28 FCT	€ 5,852.87	€ 2.00	€ 236.41	€ 5,614.46
Idelalisib 150 mg	60 FCT	€ 4,535.04	€ 2.00	€ 438.36	€ 4,094.68
Rituximab 100 mg	2 CIS	€ 748.07	€ 2.00	€ 69.93	€ 676.14
Rituximab 500 mg	1 CIS	€ 1,819.89	€ 2.00	€ 172.53	€ 1,645.36
Rituximab 500 mg	2 CIS	€ 3,639.48	€ 2.00	€ 350.68	€ 3,286.80
Venetoclax 10 mg	14 FCT	€ 86.95	€ 2.00	€ 2.99	€ 81.96
Venetoclax 50 mg	7 FCT	€ 200.46	€ 2.00	€ 7.48	€ 190.98
Venetoclax 100 mg	112 FCT	€ 5,926.27	€ 2.00	€ 239.40	€ 5,684.87
Abbreviations: FCT = film-coated tablets; HC = Hard capsules; CIS = concentrate for the preparation of an infusion solution; PIE = powder for solution for infusion, PIC = powder for the preparation of an infusion solution concentrate; DSS = dry substance without solvent					

LAUER-TAXE® last revised: 15 May 2023

<u>Costs for additionally required SHI services:</u>

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.

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

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	Costs/ patient/ year
Appropriate comparator therapy:							
Venetoclax in combination with rituximab							
Dimetindene IV (1 mg/10 kg, IV)	5 SFI each 4 mg	€ 23.67	€ 2.00	€ 5.81	€ 15.86	6.0	€ 47.58
Paracetamol[8] (1,000 mg, PO)	10 TAB each 1,000 mg	€ 3.32	€ 0.17	€ 0.14	€ 3.01	6.0	€ 3.01
Fludarabine in combination with cyclophosphamide and rituximab [FCR]							
Dimetindene IV (1 mg/10 kg, IV)	5 SFI each 4 mg	€ 23.67	€ 2.00	€ 5.81	€ 15.86	6.0	€ 47.58
Paracetamol[9] (1,000 mg, PO)	10 TAB each 1,000 mg	€ 3.32	€ 0.17	€ 0.14	€ 3.01	6.0	€ 3.01
Bendamustine in combination with rituximab [BR]							
Dimetindene IV (1 mg/10 kg, IV)	5 SFI each 4 mg	€ 23.67	€ 2.00	€ 5.81	€ 15.86	6.0	€ 47.58
Paracetamol[9] (1,000 mg, PO)	10 TAB each 1,000 mg	€ 3.32	€ 0.17	€ 0.14	€ 3.01	6.0	€ 3.01
Chlorambucil in combination with rituximab							
Dimetindene IV (1 mg/10 kg, IV)	5 SFI each 4 mg	€ 23.67	€ 2.00	€ 5.81	€ 15.86	6.0	€ 47.58
Paracetamol[9] (1,000 mg, PO)	10 TAB each 1,000 mg	€ 3.32	€ 0.17	€ 0.14	€ 3.01	6.0	€ 3.01
idelalisib in combination with rituximab							
Dimetindene IV (1 mg/10 kg, IV)	5 SFI each 4 mg	€ 23.67	€ 2.00	€ 5.81	€ 15.86	6.0	€ 47.58
Paracetamol[9] (1,000 mg, PO)	10 TAB each 1,000 mg	€ 3.32	€ 0.17	€ 0.14	€ 3.01	6.0	€ 3.01

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, rituximab and bendamustine 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

[8] Fixed reimbursement rate

hepatitis B, the costs for additionally required SHI services for tests for hepatitis B are not presented in the resolution.

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 8 February 2022, 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 07 February 2023.

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	8 February 2022	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	7 February 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	25 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 16 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