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), first-line)

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 with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, as well the addendum drawn up by the G-BA on the benefit assessment. 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 previously untreated chronic lymphocytic leukemia (CLL).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with previously untreated chronic lymphocytic leukemia (CLL)

Appropriate comparator therapy for zanubrutinib:

- Ibrutinib

or

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

- Ibrutinib in combination with rituximab or obinutuzumab

or

- Fludarabine in combination with cyclophosphamide and rituximab [FCR] (only for patients without genetic risk factors and < 65 years of age who are eligible for therapy with FCR on the basis of their general condition and comorbidities)

or

- Bendamustine in combination with rituximab (only for patients without genetic risk factors and who are ineligible for therapy with FCR according to the above criteria)

or

- Chlorambucil in combination with rituximab or obinutuzumab (only for patients without genetic risk factors and who are ineligible for therapy with FCR according to the above criteria)

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, the cytostatic agents bendamustine, chlorambucil and fludarabine; the B-cell receptor inhibitors acalabrutinib, ibrutinib and idelalisib; the BCL-2 inhibitor venetoclax; the anti-CD-20 antibodies obinutuzumab and rituximab; and the glucocorticoids prednisolone and prednisone are available for the treatment of previously untreated CLL according to the marketing authorisation. The chronic lymphocytic leukemia is a type of non-Hodgkin lymphoma. Accordingly, the active ingredients cyclophosphamide, dexamethasone, doxorubicin, etoposide, mitoxantrone, 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 the following new active ingredients according to Section 35a SGB V are available:

- Acalabrutinib (resolutions of 3 June 2021)
- Ibrutinib (resolutions of 1 April 2021, 20 February 2020, 15 December 2016 and 21 July 2016)
- Idelalisib (resolutions of 16 March 2017)
- Obinutuzumab (resolution of 4 November 2021)
- Venetoclax (resolutions of 15 October 2020 and 16 May 2019)

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

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

Chronic lymphocytic leukemia (CLL) and small-cell lymphocytic lymphoma (SLL) are considered as one entity according to the WHO classification.

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.

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.

According to both the guidelines and the written statement of the German Society for Haematology and Oncology (DGHO), a therapy based on a Bruton Tyrosine Kinase (BTK) inhibitor can be considered for patients with previously untreated CLL. This recommendation applies regardless of the presence of genetic risk factors. A marketing authorisation exists in the present therapeutic indication for the BTK inhibitor ibrutinib as monotherapy or in combination with rituximab or obinutuzumab as well as for the BTK inhibitor acalabrutinib as monotherapy or in combination with obinutuzumab.

In the benefit assessment of ibrutinib as monotherapy in the patient population which is unsuitable for chemoimmunotherapy and in which a 17p deletion or TP53 mutation is present, the G-BA identified a hint for a non-quantifiable additional benefit compared with best supportive care in its resolution of 21 July 2016. The benefit assessment of the combination ibrutinib + rituximab resulted in a hint for a considerable additional benefit for the sub-population of patients who are eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR) compared to FCR (resolution of 1 April 2021). The combination of ibrutinib + obinutuzumab was assessed by the G-BA as having a hint for a minor additional benefit compared to chlorambucil + obinutuzumab for patients who are ineligible for therapy with FCR (resolution of 1 April 2021). The combination of ibrutinib with venetoclax is a new treatment option for patients with previously untreated CLL that was approved on 02.08.2022. Based on the generally accepted state of medical knowledge, ibrutinib in combination with venetoclax is not determined to be an appropriate comparator therapy for the present resolution.

For both acalabrutinib as monotherapy and in combination with obinutuzumab, the G-BA identified a hint for a minor additional benefit compared to chlorambucil in combination with obinutuzumab for patients who do not have a 17p deletion or TP53 mutation and for whom therapy with FCR is not an option (resolutions of 3 June 2021). There are no consistent recommendations for acalabrutinib as monotherapy or acalabrutinib in combination with obinutuzumab in the available guidelines. The clinical significance of acalabrutinib cannot be conclusively assessed according to the generally recognised state of medical knowledge. Acalabrutinib both as monotherapy and in combination with obinutuzumab is not determined to be an appropriate comparator therapy for the present resolution.

According to the available evidence, in addition to BTK inhibitors, a therapy with the combination of venetoclax + obinutuzumab is also an option for patients, regardless of the presence of risk factors. In the resolutions of 15 October 2020, no additional benefit was identified for venetoclax in combination with obinutuzumab compared with the corresponding comparator therapies for the sub-populations investigated in each case. Since therapy alternatives with a proven additional benefit are available in a comparable treatment setting, the G-BA does not consider venetoclax in combination with obinutuzumab to be an appropriate comparator therapy.

For patients who do not have any genetic risk factors, chemoimmunotherapy can also be considered according to guidelines and the written statement of the scientific-medical society and the clinical experts in the written statement procedure. For patients under 65 years of age who have an appropriate general condition and who do not have any relevant comorbidities, a therapy with FCR is recommended as a priority among the chemoimmunotherapies. Chemoimmunotherapies consisting of a chemotherapeutic agent and a CD20 antibody can be considered for patients who are ineligible for therapy with FCR according to the criteria of age, general condition and comorbidities. In this respect, the focus is on the approved treatment options bendamustine in combination with rituximab (BR) as well as chlorambucil in combination with rituximab (ClbR) and chlorambucil in combination with

obinutuzumab (ClbO). By resolution of 4 November 2021, the G-BA did not identify any additional benefit for obinutuzumab in combination with chlorambucil compared with the appropriate comparator therapy.

Regarding the genetic risk factors, in addition to the already considered factors 17p and TP53 mutation, an unmutated immunoglobulin heavy chain variable (IGHV) region and a complex karyotype can also be found in the guidelines and the written statement of the scientific-medical society. Compared to the other risk factors, the complex karyotype is not given the same importance in the evidence. Accordingly, the G-BA considers genetic risk factors: Presence of a 17p deletion / TP53 mutation or an unmutated immunoglobulin heavy chain variable region (IGHV).

According to the recommendations from guidelines and taking into account the respective authorisation status, the therapy options ibrutinib as monotherapy or in combination with rituximab or obinutuzumab, fludarabine in combination with cyclophosphamide and rituximab (FCR), bendamustine in combination with rituximab [BR], chlorambucil in combination with rituximab (ClbR) or chlorambucil in combination with obinutuzumab (ClbO) are determined as appropriate comparator therapies.

The appropriate comparator therapy determined here includes several therapeutic alternatives. In this context, individual therapeutic alternatives only represent a comparator therapy for the part of the patient population that has the patient and disease characteristics specified in brackets. The therapeutic alternatives are only to be considered equally appropriate in the therapeutic indication, where the patient populations have the same characteristics.

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

The pharmaceutical company only submits data on a sub-population in the therapeutic indication, which is why two patient populations are formed for the present resolution:

a) Adults with previously untreated chronic lymphocytic leukemia (CLL) without the presence of genetic risk factors who are ineligible for therapy with FCR on the basis of their general condition and comorbidities

b) Adults with previously untreated chronic lymphocytic leukemia (CLL) without genetic risk factors who are eligible for therapy with FCR on the basis of their general condition and comorbidities and adults with previously untreated chronic lymphocytic leukemia (CLL) with genetic risk factors

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

a) Adults with previously untreated chronic lymphocytic leukemia (CLL) without the presence of genetic risk factors who are ineligible for therapy with FCR on the basis of their general condition and comorbidities

Hint for a minor additional benefit

Justification:

The benefit assessment is based on the results of the randomised, open-label, ongoing phase III SEQUOIA study. The study compares zanubrutinib with bendamustine in combination with rituximab (BR).

Adults with previously untreated and treatment-naive cluster-of-differentiation (CD)-20 positive CLL or small cell lymphocytic lymphoma (SLL) according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria were enrolled. It was assumed that patients were ineligible for FCR therapy, which is why only patients who were ≥ 65 years of age or younger patients who had either a Cumulative Illness Rating Scale (CIRS) score > 6 and/or a creatinine clearance < 70 ml/min and/or a history of severe infection or multiple infections within the last 2 years were enrolled.

Patients in the SEQUOIA study were assigned to one of 4 cohorts, with the active controlled part of the study (comparison versus bendamustine in combination with rituximab) comprising cohorts 1 and 1a. These two cohorts included patients without a deletion in the short arm of chromosome 17 (17p deletion); cohort 1a includes only patients from Chinese study sites.

The pharmaceutical company submits the data of a sub-population of the cohort 1 for the present benefit assessment. These are patients who do not have a TP53 mutation but show a mutated IGHV status.

In the cohort 1, a total of 479 patients were randomised to the two treatment arms (test arm: N = 241, control arm: N = 238). Stratification was by age (< 65 years vs ≥ 65 years), stage of the disease (Binet stage C vs A or B), immunoglobulin heavy chain variable region (IGHV) mutation status (unmutated vs mutated) and region (North America vs Europe vs Asia-Pacific).

The submitted sub-population includes 104 patients in the intervention arm and 106 in the control arm. Patient characteristics are predominantly balanced between the two treatment arms. The patients were on average 70 years old and had an Eastern Cooperative Oncology Group - Performance Status (ECOG-PS) of ≤ 2, with the majority having an ECOG-PS of 0 or 1.

Patients in the intervention arm of the SEQUOIA study were treated until disease progression, unacceptable toxicity, withdrawal of consent or end of the study. The treatment with zanubrutinib (oral application) largely complied with the requirements in zanubrutinib's product information.

In the control arm, patients were treated for a maximum of six cycles (28 days each). The treatment with rituximab (intravenous application) was also largely carried out according to the product information. For the treatment with bendamustine (intravenous application), there are no specific dosage recommendations in the product information, but the procedure

in the SEQUOIA study corresponds to the procedure of the studies conducted on the combination of bendamustine and rituximab in the therapeutic indication.

The SEQUOIA study was launched in October 2017 and has not yet been completed. It was conducted at 153 study sites in 16 countries across Europe, North America, Asia and Australia, with the majority of patients of the submitted sub-population being of European descent (71% in the test arm, 70% in the control arm).

There are a total of three data cut-offs in the dossier:

- Data cut-off from 7 May 2021 (predefined interim analysis of PFS after 107 events in cohort 1)
- Data cut-off from 7 September 2021 (predefined interim analysis of overall survival at the time originally expected for the final analysis of PFS)
- Data cut-off from 7 March 2022 (follow-up data for overall survival; requested data cut-off from the Food and Drug Administration (FDA))

For the present benefit assessment, the data cut-off from 7 March 2022 is used, for which data on all patient-relevant endpoints are available.

Relevant sub-population

As already described above, a sub-population of cohort 1 with patients who do not have a TP53 mutation but show a mutated IGHV status was submitted by the pharmaceutical company. In the view of the G-BA, the pharmaceutical company's procedure for forming this sub-population is fundamentally appropriate and the sub-population formed is appropriate to represent patients in the therapeutic indication who are eligible for therapy with BR.

In principle, however, the patients of cohort 1a who do not have a TP53 mutation but show a mutated IGHV status also represent a relevant sub-population in the present therapeutic indication. Due to the low percentage of patients in cohort 1a in the total number of cohort 1, it is assumed that the relevant sub-population of cohort 1a has no influence on the outcome of this benefit assessment.

Extent and probability of the additional benefit

Mortality

Overall survival was defined in the SEQUOIA study as the time from randomisation to death, regardless of the underlying cause.

For the endpoint of overall survival, no statistically significant difference was detected between zanubrutinib and BR.

Thus, no advantage or disadvantage of zanubrutinib over BR can be determined for overall survival.

Morbidity

Progression-free survival

Progression-free survival (PFS) is the primary endpoint of the SEQUOIA study. It is defined as the time from randomisation to the first documented disease progression or death, whichever came first. The PFS was collected by the principal investigator, the evaluation was performed blinded by an ICR (Independent Central Review) according to the modified iwCLL

(International Workshop Group on CLL) criteria with modified explanation for treatment-related lymphocytosis in patients with CLL and evaluated according to the modified Lugano classification in patients with SLL.

Prolongation of PFS is statistically significantly with zanubrutinib compared to BR.

The PFS endpoint is a combined endpoint composed of endpoints of the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The morbidity component "Disease progression" is not assessed according to symptoms but 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 additional benefit remains unaffected.

Symptomatology

Symptomatology was assessed in the SEQUOIA study using the symptom scales of the EORTC QLQ-C30 questionnaire.

There was no statistically significant difference between zanubrutinib and BR for any of the endpoints of the questionnaire for symptomatology.

Health status

The health status is assessed in the SEQUOIA study using the EQ-5D visual analogue scale (VAS).

For the endpoint of health status, there is no statistically significant difference between zanubrutinib and BR.

In the overall analysis of the morbidity results, neither advantages nor disadvantages of zanubrutinib are found.

Quality of life

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

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

There is a statistically significant difference between the treatment arms to the advantage of zanubrutinib solely for the endpoint of role functioning.

In the overall analysis of the results, neither an advantage nor a disadvantage of zanubrutinib is found with regard to health-related quality of life.

Side effects

With the dossier, the pharmaceutical company submits analyses on the side effects, on the basis of which statements can only be made on the first 8 months of the therapy due to strongly differing observation times between the treatment arms.

Within the framework of the written statement procedure, the pharmaceutical company submitted supplementary analyses in this regard for the period up to 30 days (zanubrutinib) or 90 days (BR) after the last dose or until disease progression, whichever was later. The median observation durations between the intervention and comparator arms are comparable. The data subsequently submitted are used for the benefit assessment. Subgroup analyses on the data subsequently submitted were not submitted.

Adverse events in total

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

Serious AEs (SAEs)

For the endpoint of SAEs, there is no statistically significant difference between the treatment groups.

Severe AEs

For the endpoint of severe AEs (CTCAE grade ≥ 3), there is a statistically significant difference to the advantage of zanubrutinib compared to BR.

Discontinuation due to AEs

The results from the dossier are used for the endpoint of discontinuation due to adverse events as this endpoint in the present data basis only includes events that occurred during the duration of treatment with the study medication. Due to the time-limited treatment duration in the comparator arm of the SEQUOIA study, the median treatment and observation durations differ for this endpoint. The data can thus only be interpreted for the first 8 months.

There is a statistically significant difference to the advantage of zanubrutinib compared to BR.

Specific AEs

For the endpoints of fever (SAEs), blood and lymphatic system disorders (severe AEs) and investigations (severe AEs) as well as nausea (AEs) and hypotension (AEs), there is a statistically significant difference between the treatment groups to the advantage of zanubrutinib.

For the endpoint of bleeding (AEs) and contusion (AEs), there is a statistically significant difference between the treatment arms to the disadvantage of zanubrutinib.

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

No suitable data are available for the endpoint of infusion-related reactions as no comparator data were collected for this endpoint due to the open-label study design (without placebo infusion) and regular intravenous administration only in the comparator arm versus oral administration in the intervention arm.

In the overall assessment of side effects, zanubrutinib has advantages over BR in the overall categories of severe AEs (CTCAE ≥ 3) and discontinuation due to AEs, as well as predominantly in detail for specific AEs. Overall, this is assessed as a relevant improvement in side effects.

Overall assessment/ conclusion

The benefit assessment of zanubrutinib as monotherapy for the treatment of adults with previously untreated chronic lymphocytic leukemia (CLL) without genetic risk factors who are ineligible for therapy with FCR is based on results of the SEQUOIA study on the endpoint categories of mortality, morbidity, health-related quality of life and side effects in comparison with bendamustine in combination with rituximab.

For the endpoint of overall survival, there are neither advantages nor disadvantages of zanubrutinib.

For the endpoint categories of morbidity and health-related quality of life, there are also no advantages or disadvantages of zanubrutinib compared to BR.

In the overall assessment of side effects, zanubrutinib has advantages over BR in the overall categories of severe AEs (CTCAE ≥ 3) and discontinuation due to AEs, as well as predominantly in detail for specific AEs. Overall, this is assessed as a relevant improvement in side effects.

In summary, there is a relevant improvement in side effects. There are no relevant differences in the patient-relevant endpoints of overall survival, morbidity and health-related quality of life.

In the overall analysis, the G-BA comes to the conclusion that there is a minor additional benefit of zanubrutinib compared to BR.

Reliability of data (probability of additional benefit)

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

The risk of bias at study level is rated as low.

For the endpoint of overall survival, a low risk of bias is assumed.

For the patient-reported endpoints of symptomatology, health status and health-related quality of life as well as for the endpoint of discontinuation due to AEs, the risk of bias is rated as high due to the open-label study design.

The risk of bias in the results of the endpoints of SAEs, severe AEs, specific AEs and specific severe AEs is rated as low. However, there is considerable uncertainty due to the lack of subgroup analyses for the subsequently submitted evaluations on side effects, which are necessary for fully comprehensive weighing of the additional benefit.

Overall, a hint is derived for the reliability of data of the additional benefit identified.

b) Adults with previously untreated chronic lymphocytic leukemia (CLL) without genetic risk factors who are eligible for therapy with FCR on the basis of their general condition and comorbidities and adults with previously untreated chronic lymphocytic leukemia (CLL) with genetic risk factors

An additional benefit is not proven.

Justification:

For adults with previously untreated chronic lymphocytic leukemia (CLL) with genetic risk factors and adults with previously untreated chronic lymphocytic leukemia (CLL) without genetic risk factors who are eligible for therapy with FCR on the basis of their general condition and comorbidities, the pharmaceutical company does not submit any data for the assessment of the additional benefit. Thus, an additional benefit compared to the appropriate comparator therapy 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 previously untreated chronic lymphocytic leukemia (CLL). In the therapeutic indication under consideration, the appropriate comparator therapy was determined as follows:

Adults with previously untreated chronic lymphocytic leukemia (CLL)

The appropriate comparator therapy includes monotherapy with ibrutinib and combination therapy of ibrutinib in combination with rituximab or obinutuzumab, as well as chemoimmunotherapy with FCR, BR, ClbR or ClbO, with limitations for certain patients.

The pharmaceutical company only submits data on one sub-population in the therapeutic indication, which is why two sub-populations are formed for the present resolution:

a) Adults with previously untreated chronic lymphocytic leukemia (CLL) without the presence of genetic risk factors who are ineligible for therapy with FCR on the basis of their general condition and comorbidities

b) Adults with previously untreated chronic lymphocytic leukemia (CLL) without genetic risk factors who are eligible for therapy with FCR on the basis of their general condition and comorbidities and adults with previously untreated chronic lymphocytic leukemia (CLL) with genetic risk factors

About patient group a)

The pharmaceutical company submits data from a sub-population of the SEQUOIA study comparing zanubrutinib with BR.

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, there are also neither advantages nor disadvantages.

In the overall assessment of side effects, zanubrutinib has advantages over BR in the overall categories of severe AEs (CTCAE ≥ 3) and discontinuation due to AEs, as well as predominantly in detail for specific AEs. Overall, this is assessed as a relevant improvement in side effects.

In summary, there is a relevant improvement in side effects. There are no relevant differences in the patient-relevant endpoints of overall survival, morbidity and health-related quality of life.

In the overall analysis, a minor additional benefit of zanubrutinib is identified.

Due to the open-label study design and the lack of subgroup analyses, the reliability of data of the subsequently submitted evaluations on the side effects is classified as a hint.

In the overall assessment, a hint for a minor additional benefit over BR is identified.

About patient group b)

No data are available to allow an assessment of the additional benefit. An additional benefit compared to the appropriate comparator therapy is therefore not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

Adults with previously untreated chronic lymphocytic leukemia (CLL)

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. In relation to the total population of all adults with newly diagnosed CLL, the information provided by the pharmaceutical company is plausible in the order of magnitude - with minor uncertainties.

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

Adults with previously untreated chronic lymphocytic leukemia (CLL)

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 Fischer K. et al.[5], Eichhorst, B., et al.[4], and Goede, V., et al.[6] were used for the cost representation of fludarabine in combination with cyclophosphamide and rituximab, bendamustine in combination with rituximab as well as chlorambucil in combination with rituximab against the background of the lack of information on dosage 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.

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Zanubrutinib	Continuously, 1 x daily or Continuously, 2 x daily	365.0	1	365.0
Appropriate comparator therapy				
Ibrutinib monotherapy				
Ibrutinib	Continuously, 1 x daily	365.0	1	365.0
Ibrutinib in combination with rituximab				
Ibrutinib	Continuously, 1 x daily	365.0	1	365.0
Rituximab[2]	Cycle 1: Day 1 and 2 Cycle 2 - 6: Day 1 28-day cycle	6.0	Cycle 1: 2 Cycle 2 - 6: 1	7.0
Ibrutinib in combination with obinutuzumab				
Ibrutinib	Continuously, 1 x daily	365.0	1	365.0
Obinutuzumab	every 28 days on	6.0	Cycle 1:	9.0

[2] In cycle 1, the rituximab dose is administered on 2 days (50 mg/m² on day 1, 325 mg/m² on day 2)

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	day 1 + 2, 8 and 15 of cycle 1 and on day 1 of cycle 2 - 6[3]		4 Cycle 2 - 6: 1	
Fludarabine in combination with cyclophosphamide and rituximab [FCR][4]				
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 in combination with rituximab[5]				
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
Chlorambucil in combination with rituximab[6]				
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
Chlorambucil in combination with obinutuzumab				
Chlorambucil	Day 1 and 15 of a 28-day cycle	6.0	2	12.0
Obinutuzumab	Cycle 1: Day 1 + 2, 8 and 15 Cycle 2 - 6: Day 1 of a 28-day cycle each	6.0	Cycle 1: 4 Cycle 2 - 6: 1	9.0

[3] The first dose of obinutuzumab was divided between day 1 (100 mg) and day 2 (900 mg).

[4] Eichhorst, B., et al., First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukemia (CLL10): Lancet Oncol. 2016 Jul;17(7):928-942

[5] Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicentre phase II trial of the German Chronic Lymphocytic Leukemia Study Group.
J Clin Oncol. 2012 Sep 10;30(26):3209-16
https://ascopubs.org/doi/10.1200/JCO.2011.39.2688

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

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements of 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.

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 or 160 mg	320 mg	4 x 80 mg	365.0	1460 x 80 mg
Appropriate comparator therapy					
Ibrutinib monotherapy					
Ibrutinib	420 mg	420 mg	1 x 420 mg	365.0	365 x 420 mg
Ibrutinib in combination with rituximab					
Ibrutinib	420 mg	420 mg	1 x 420 mg	365.0	365 x 420 mg
Rituximab	Cycle 1 Day 1: 50 mg/m² = 95 mg Day 2: 325 mg/m² = 617.5 mg Cycle 2 - 6: 500 mg/m² = 950 mg	Cycle 1 Day 1: 95 mg Day 2: 617.5 mg Cycle 2 - 6: 950 mg	Cycle 1 Day 1: 1 x 100 mg Day 2: 2 x 100 mg + 1 x 500 mg Cycle 2 - 6: 2 x 500 mg	7.0	3 x 100 mg + 11 x 500 mg
Ibrutinib in combination with obinutuzumab					
Ibrutinib	420 mg	420 mg	1 x 420 mg	365.0	365 x 420 mg
Obinutuzumab	Cycle 1	Cycle 1	1 x 1,000 mg	9.0	8 x 1,000 mg

[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
	Day 1: 100 mg Day 2: 900 mg Day 8 + 15: 1000 mg <u>Cycle 2 - 6</u> Day 1: 1000 mg	Day 1: 100 mg Day 2: 900 mg Day 8 + 15: 1000 mg <u>Cycle 2 - 6</u> Day 1: 1000 mg			
Fludarabine in combination with cyclophosphamide and rituximab [FCR]					
Fludarabine	25 mg/m^2 = 47.5 mg	47.5 mg	1 x 50 mg	18.0	18 x 50 mg
Cyclophosphamide	250 mg/m^2 = 475 mg	475 mg	1 x 500 mg	18.0	18 x 500 mg
Rituximab	<u>Cycle 1:</u> 375 mg/m^2 = 712.5 mg <u>Cycle 2 - 6</u> Day 1: 500 mg/m^2 = 950 mg	<u>Cycle 1:</u> 712.5 mg <u>Cycle 2 - 6</u> Day 1: 950 mg	<u>Cycle 1:</u> 3 x 100 mg 1 x 500 mg <u>Cycle 2 - 6</u> Day 1: 2 x 500 mg	6.0	3 x 100 mg + 11 x 500 mg
Bendamustine in combination with rituximab [BR]					
Bendamustine	90 mg/m^2 = 171 mg	171 mg	1 x 100 mg + 3 x 25 mg	12.0	12 x 100 mg + 36 x 25 mg
Rituximab	<u>Cycle 1:</u> 375 mg/m^2 = 712.5 mg <u>Cycle 2 - 6:</u> 500 mg/m^2 = 950 mg	<u>Cycle 1:</u> 712.5 mg <u>Cycle 2 - 6:</u> 950 mg	<u>Cycle 1:</u> 3 x 100 mg 1 x 500 mg <u>Cycle 2 - 6</u>: 2 x 500 mg	6.0	3 x 100 mg + 11 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	<u>Cycle 1:</u> 375 mg/m^2 = 712.5 mg	<u>Cycle 1:</u> 712.5 mg	<u>Cycle 1:</u> 3 x 100 mg 1 x 500 mg	6.0	3 x 100 mg + 11 x 500 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	Cycle 2 - 6: 500 mg/m^2 = 950 mg	Cycle 2 - 6: 950 mg	Cycle 2 - 6: 2 x 500 mg		
Chlorambucil in combination with obinutuzumab					
Chlorambucil	0.5 mg/kg = 38.5 mg	38.5 mg	19 x 2 mg	12.0	228 x 2 mg
Obinutuzumab	Cycle 1 Day 1: 100 mg Day 2: 900 mg Day 8 + 15: 1000 mg Cycle 2 - 6 Day 1: 1000 mg	Cycle 1 Day 1: 100 mg Day 2: 900 mg Day 8 + 15: 1000 mg Cycle 2 - 6 Day 1: 1000 mg	1 x 1,000 mg	9.0	8 x 1,000 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with 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 80 mg	120 HC	€ 5,995.07	€ 2.00	€ 581.30	€ 5,411.77
Appropriate comparator therapy					
Ibrutinib 420 mg	28 FCT	€ 5,852.87	€ 2.00	€ 236.41	€ 5,614.46
Rituximab 100 mg	2 CIS	€ 748.07	€ 2.00	€ 69.93	€ 676.14
Rituximab 500 mg	2 CIS	€ 3,639.48	€ 2.00	€ 350.68	€ 3,286.80
Rituximab 500 mg	1 CIS	€ 1,819.89	€ 2.00	€ 172.53	€ 1,645.36
Obinutuzumab 1000 mg	1 CIS	€ 2,649.21	€ 2.00	€ 253.73	€ 2,393.48
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
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
Chlorambucil 2 mg	50 FCT	€ 37.73	€ 2.00	€ 2.51	€ 33.22
Abbreviations: HC = hard capsules, FCT = film-coated tablets, CIS = concentrate for the preparation of an infusion solution, PSI = powder for solution for injection, PIC = powder for the preparation of an infusion solution concentrate, DSS = dry substance without solvent					

LAUER-TAXE® last revised: 15 May 2023

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.

Premedication:

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 as well as obinutuzumab (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:							
Ibrutinib in combination with rituximab							
Dimetindene IV (1 mg/10 kg, IV)	5 SFI each 4 mg	€ 23.67	€ 2.00	€ 5.81	€ 15.86	7.0	€ 47.58
Paracetamol[8] (1,000 mg, PO)	10 TAB each 1,000 mg	€ 3.32	€ 0.17	€ 0.14	€ 3.01	7.0	€ 3.01
Ibrutinib in combination with obinutuzumab							
Dimetindene IV (1 mg/10 kg, IV)	5 SFI each 4 mg	€ 23.67	€ 2.00	€ 5.81	€ 15.86	9.0	€ 63.44
Paracetamol[8] (1,000 mg, PO)	10 TAB each 1,000 mg	€ 3.32	€ 0.17	€ 0.14	€ 3.01	9.0	€ 3.01
Dexamethasone[8] IV 5 x 4 mg	10 SFI each 4 mg	€ 16.89	€ 2.00	€ 0.44	€ 14.45	9.0	€ 72.25
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[8] (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[8] (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[8] (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 obinutuzumab							
Dimetindene IV (1 mg/10 kg, IV)	5 SFI each 4 mg	€ 23.67	€ 2.00	€ 5.81	€ 15.86	9.0	€ 63.44

[8] Fixed reimbursement rate

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
Paracetamol[8] (1,000 mg, PO)	10 TAB each 1,000 mg	€ 3.32	€ 0.17	€ 0.14	€ 3.01	9.0	€ 3.01
Dexamethasone [8] (IV 5 x 4 mg)	10 SFI each 4 mg	€ 16.89	€ 2.00	€ 0.44	€ 14.45	9.0	€ 72.25

Patients should be tested for HBV infection before starting treatment with zanubrutinib. These examinations are also required when using ibrutinib, rituximab, bendamustine and obinutuzumab 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.

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.

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 1, sentence 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.

By letter dated 3 May 2023, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 26 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
Working group Section 35a	18 April 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	2 May 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	9 May 2023 30 May 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	6 June 2023	Concluding discussion of the draft resolution
Plenum	15 June 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 June 2023

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

Prof. Hecken