Gemeinsamer Bundesausschuss

Justification

to 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 Pirtobrutinib (new therapeutic indication: chronic lymphocytic leukaemia (CLL), relapsed or refractory, monotherapy)

of 2 October 2025

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess the benefit of all 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 studies the pharmaceutical company have 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 decide on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was on 15 April 2025 in accordance with Chapter 5 Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 2 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 2 VerfO on 4 April 2025.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 July 2025 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 pirtobrutinib 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. In order to

determine the extent of the additional benefit, the G-BA have 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 pirtobrutinib.

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 Pirtobrutinib (Jaypirca) in accordance with the product information

Jaypirca as monotherapy is indicated for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a BTK inhibitor.

Therapeutic indication of the resolution (resolution of 2 October 2025):

See the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi) and not with a B-cell lymphoma-2 (BCL-2) inhibitor

Appropriate comparator therapy for pirtobrutinib as monotherapy:

- Venetoclax in combination with rituximab

b) Adults with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi) and with a B-cell lymphoma-2 (BCL-2) inhibitor

Appropriate comparator therapy for pirtobrutinib as monotherapy:

Individualised therapy with selection of

- idelalisib in combination with rituximab,
- venetoclax in combination with rituximab and
- bendamustine in combination with rituximab

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

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

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

On 1. In addition to pirtobrutinib, according to the authorisation status, the cytostatic agents chlorambucil, cyclophosphamide and fludarabine; the BTK inhibitors acalabrutinib, ibrutinib and zanubrutinib; the BCL-2 inhibitor venetoclax; the PI3K inhibitors idelalisib and duvelisib[2]; the anti-CD-20 antibody rituximab and the glucocorticoids prednisolone and prednisone are available for the treatment of relapsed/ refractory chronic lymphocytic leukaemia.

The chronic lymphocytic leukaemia is a type of non-Hodgkin lymphoma. Accordingly, the active ingredients bendamustine, bleomycin, carmustine, cytarabine, dexamethasone, doxorubicin, etoposide, ifosfamide, methotrexate, mitoxantrone, trofosfamide, vinblastine, vincristine and vindesine 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.

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:

- Zanubrutinib (resolution of 15 June 2023)
- Duvelisib (resolution of 21 July 2022)
- Acalabrutinib (resolution of 5 August 2021)
- Venetoclax (resolution of 16 May 2019)
- Ibrutinib (resolutions of 16 March 2017 and 21 July 2016)
- Idelalisib (resolutions of 16 March 2017 and 15 September 2016)

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

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

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

For the present therapeutic indication, it is presumed that the patients are in need of treatment (for example, stage C Binet).

[2] Currently not available on the German market

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 leukaemia (CLL), wherein these patient populations are differentiated depending on the prior therapy/ therapies - specifically with a BTK inhibitor and/or BCL-2 inhibitor:

On patient population a):

The available guidelines and the written statement of the AkdÄ indicate that venetoclax + rituximab is the preferred therapy standard for patients with BTK inhibitor pretreatment from the second-line therapy onwards due to its high efficacy and the limited treatment duration.

In the benefit assessment, an indication of a minor additional benefit of venetoclax in combination with rituximab compared to bendamustine + rituximab was identified 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 is the individualised appropriate therapy (resolution of 16 May 2019). No data on the other patient populations were available, which is why an additional benefit could not be derived here. Overall, taking into account the guideline recommendations, the G-BA considers venetoclax in combination with rituximab to be an appropriate comparator therapy for relapsed or refractory patients who have previously been treated with a BTK inhibitor and not with a BCL-2 inhibitor.

On patient population b):

The available guidelines and the written statement of the AkdÄ indicate that the therapy of patients who have already received two prior therapies, including a BTK inhibitor and a BCL-2 inhibitor, is characterised by individualised treatment decisions. The treatment decision is made in particular taking into account the previous therapy, the response, the genetic risk factors and the duration of remission of the previous therapies and the general condition. According to the current state of medical knowledge, the presence of a 17p deletion/ TP53 mutation and an unmutated IGHV status and complex karyotype are considered genetic risk factors.

For the treatment of patients with relapsed/refractory CLL, various therapy options are mentioned in these guidelines and in the written statement of the AkdÄ. Temporary venetoclax-based treatment is recommended in preference to chemoimmunotherapy. The PI3K inhibitor idelalisib is only recommended as a lower priority due to its side effect profile. However, idelalisib in combination with rituximab is a suitable option as the patients have already received BTK inhibitors and BCL-2 inhibitors.

In the benefit assessment of idelalisib in combination with rituximab, an additional benefit was not proven in all patient groups, as no relevant data were available for the assessment of the additional benefit (resolution of 15 September 2016). No additional benefit of the combination therapy of idelalisib and ofatumumab was identified for patients with at least one prior therapy, as no relevant data were available for the assessment of the additional benefit (resolution of 16 March 2017). The present guidelines and the written statement of AkdÄ unanimously refer to the combination therapy of idelalisib with rituximab as a relevant therapy option and not to idelalisib with ofatumumab for the present patient group. In the context of individualised therapy, the G-BA therefore only considers idelalisib + rituximab to be part of the appropriate comparator therapy.

According to the present guidelines, retreatment with venetoclax + rituximab can be considered for patients already receiving BTK inhibitor and BCL-2 inhibitor if the

patients have been in remission for at least 12 months after venetoclax-based therapy. Based on the guideline recommendations and the benefit assessments presented above, the G-BA has determined venetoclax + rituximab to be an option within the individualised therapy.

Furthermore, according to the available evidence, the approved chemoimmunotherapy of bendamustine in combination with rituximab can be considered as an additional treatment option. Although chemoimmunotherapy is only recommended in exceptional cases in the available guidelines, the approved chemoimmunotherapy of bendamustine in combination with rituximab is designated by the G-BA as a component of the individualised therapy due to the limited number of therapy options for patients who have been pretreated with both BCL-2 and BTK inhibitors.

The guidelines also indicate that allogeneic stem cell transplantation can be considered a possible treatment option for suitable patients with documented therapy failure of two different signalling pathway inhibitor classes (BTK inhibitors and BCL-2 inhibitors), especially in the presence of genetic risk factors (e.g. TP53, complex karyotype). The written statement of AkdÄ also refers to the fact that allogeneic stem cell transplantation is still considered a "last-line" therapy option. The G-BA do not include allogeneic stem cell transplantation as a component of the appropriate comparator therapy since allogeneic stem cell transplantation is only considered in individual cases and only after remission induction for selected patients.

In the overall assessment, the G-BA sees the treatment options of idelalisib in combination with rituximab, venetoclax in combination with rituximab and bendamustine in combination with rituximab as options in the context of individualised therapy.

Individualised therapy is based on the assumption that several treatment options, which allow an individualised medical treatment decision, are available.

In particular, the previous therapy, the response, genetic risk factors, the duration of remission from previous therapies and the patient's general condition must be taken into account when making the treatment decision.

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 pirtobrutinib is assessed as follows:

a) Adults with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi) and not with a B-cell lymphoma-2 (BCL-2) inhibitor

An additional benefit is not proven.

Justification:

The pharmaceutical company did not submit any suitable data for the benefit assessment of this patient population. An additional benefit is therefore not proven.

b) Adults with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi) and with a B-cell lymphoma-2 (BCL-2) inhibitor

b1) Adults with relapsed or refractory chronic lymphocytic leukaemia (CLL), who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi) and with a B-cell lymphoma-2 (BCL-2) inhibitor and for whom idelalisib + rituximab or bendamustine + rituximab is the appropriate individualised therapy

Hint for a minor additional benefit

b2) Adults with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi) and with a B-cell lymphoma-2 (BCL-2) inhibitor and for whom venetoclax + rituximab is the appropriate individualised therapy

An additional benefit is not proven.

Justification:

The pharmaceutical company has submitted results from the open-label, randomised, controlled phase III BRUIN CLL-321 study for the benefit assessment.

The ongoing BRUIN CLL-321 study compares pirtobrutinib with an individualised therapy with selection of idelalisib in combination with rituximab or bendamustine in combination with rituximab. The study has been conducted in 200 study sites across Australia, Europe, Asia and North America since 2021.

Adult patients requiring treatment and patients with CLL or small cell lymphocytic lymphoma (SLL) who were pretreated with a BTK inhibitor were enrolled in the study.

A total of 238 patients were enrolled in the study and randomised in a 1:1 ratio to the two study arms (N=119 intervention arm; N=119 comparator arm). The 238 patients in total were stratified according to 17p deletion status (yes versus no) and venetoclax pretreatment (yes versus no). After disease progression, patients from the comparator arm were able to switch to treatment with pirtobrutinib (treatment switching). For the benefit assessment, the pharmaceutical company presented a sub-population of those patients who had already been pretreated with a BCL-2 inhibitor in addition to a BTK inhibitor (N=60 intervention arm; N=62 comparator arm). Within the comparator arm, 48 patients received idelalisib in combination with rituximab and 14 received bendamustine in combination with rituximab.

A total of 3 data cut-offs have been carried out for the BRUIN CLL-321 study to date:

- 29.08.2023: pre-specified final data cut-off for the PFS endpoint after approximately 88 events
- 09.02.2024: data cut-off submitted as part of the marketing authorisation according to the pharmaceutical company

- 29.08.2024: After the presence of the 1st data cut-off, final data cut-off - pre-specified in version 3 of the statistical analysis plan dated 06.09.2023 - for the overall survival endpoint after approximately 70 events about 1 year after the 1st data cut-off

For the present benefit assessment, the results for the sub-population at the data cut-off from 29.08.2024 are used.

On the implementation of the individualised therapy

For the patient population b), the G-BA determined an individualised therapy with selection of idelalisib in combination with rituximab, venetoclax in combination with rituximab or bendamustine in combination with rituximab. In the BRUIN CLL-321 study, only idelalisib in combination with rituximab and bendamustine in combination with rituximab were available to the principal investigators, but not venetoclax in combination with rituximab. In the sub-population presented by the pharmaceutical company, almost all patients (with the exception of 2 patients) had already received prior therapy with venetoclax.

It is clear from the available guidelines and the written statement of the scientific-medical societies that the choice of suitable therapy options is limited, particularly in the 3rd line of therapy, and recommendations for an optimal therapy sequence can only be made to a limited extent.

According to current guideline recommendations[3], retreatment with venetoclax may be particularly useful after a longer duration of remission (>2-3 years). However, the dossier submitted by the pharmaceutical company did not provide any information on how much time had passed since the patients in the sub-population had been treated with venetoclax or whether and for how long the patients had been in remission. It is therefore unclear whether retreatment with venetoclax in combination with rituximab would have been a relevant option for these patients.

With regard to the study population of the BRUIN CLL-321 study, the selection of idelalisib + rituximab and bendamustine + rituximab is considered to be a sufficient implementation of individualised therapy with regard to these treatment options, despite remaining uncertainties.

However, the study results only allow conclusions to be drawn for those patients who had an indication for idelalisib in combination with rituximab or bendamustine in combination with rituximab.

Thus, the results of the BRUIN CLL-321 study cannot be used for the assessment of the additional benefit in the entire sub-population b). For these reasons, the G-BA therefore considers it appropriate to subdivide the patient population b) according to the data basis for the assessment of the additional benefit: Patients for whom idelalisib in combination with rituximab or bendamustine in combination with rituximab is the appropriate individualised therapy (sub-population b1) and patients for whom venetoclax in combination with rituximab is the appropriate individualised therapy (sub-population b2).

[3] Guideline programme in oncology. S3 guideline Diagnostics, therapy and after-care for patients with chronic lymphocytic leukaemia (CLL) [online]. 2024 [accessed: 11.09.2025]. www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/CLL/Version_2/LL_CLL_Langversion_2.0.pdf.

Extent and probability of the additional benefit

b1) Adults with relapsed or refractory chronic lymphocytic leukaemia (CLL), who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi) and with a B-cell lymphoma-2 (BCL-2) inhibitor and for whom idelalisib + rituximab or bendamustine + rituximab is the appropriate individualised therapy

Mortality

Overall survival

The endpoint of overall survival was defined in the BRUIN CLL-321 study as the time from randomisation to death from any cause. There was no statistically significant difference between the treatment arms.

Morbidity

Progression-free survival (PFS)

In the BRUIN CLL-321 study, progression-free survival is operationalised as the time from randomisation to the occurrence of documented disease progression according to the iwCLL 2018 criteria or death from any cause in the absence of documented progressive disease.

The present PFS endpoint is a composite endpoint consisting of endpoints from 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" was assessed according to iwCLL 2018 criteria and thus, not in a symptom-related manner but only 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.

EORTC-QLQ C30 and health status according to EQ-5D VAS

In the BRUIN CLL-321 study, disease symptomatology was assessed using the cancer-specific EORTC-QLQ C30 questionnaire. The health status was assessed in the present study using the visual analogue scale (VAS) of the EQ-5D. The data are unsuitable, as the return rates for all questionnaires, particularly in the control arm, fall early on and differ greatly between the study arms. As only a few events occurred at the early survey time points, this means that the results of the PROs cannot be interpreted overall.

Quality of life

EORTC-QLQ C30

Health-related quality of life is assessed in the BRUIN CLL-321 study using the functional scales of the EORTC-QLQ C30. The data are unsuitable, as the return rates for all questionnaires, particularly in the control arm, fall early on and differ greatly between the study arms. As only a few events occurred at the early survey time points, this means that the results of the PROs cannot be interpreted overall.

Side effects

Endpoints in the category side effects were assessed up to 28 days after the end of treatment.

Adverse events (AEs) in total

Nearly all study participants experienced an adverse event. These are only presented additionally.

Serious adverse events (SAEs)

For the endpoint of SAEs, there was no statistically significant difference between the treatment arms of the study.

Severe AEs

For the endpoint of severe AEs, there was a statistically significant difference to the advantage of pirtobrutinib.

However, there was an effect modification due to the Rai stage characteristic. There was an advantage of pirtobrutinib for patients in Rai stage 0-II, while there was no significant difference for patients in Rai stage III-IV. In view of the fact that this effect modification is only shown for one endpoint, the result for the total population is used for the assessment.

Discontinuation due to AEs

For the endpoint of discontinuation due to AEs, the study showed a statistically significant difference to the advantage of pirtobrutinib.

Specific adverse events:

Infections and infestations (AEs) and cardiac disorders (AEs)

For each of the endpoints of infections and infestations as well as cardiac disorders, there was no statistically significant difference between the treatment arms.

Bleeding (severe AEs, AEs)

No suitable data are available for the bleeding endpoint (severe AEs and AEs).

Other specific AEs

For each of the other specific AEs: bronchitis, fever, injury, poisoning and procedural complications, renal and urinary disorders, diarrhoea, investigations, skin and subcutaneous tissue disorders, metabolism and nutrition disorders, hepatobiliary disorders as well as vascular disorders, the study showed statistically significant differences to the advantage of pirtobrutinib.

Conclusion on side effects:

In the overall assessment, there were statistically significant differences to the advantage of pirtobrutinib for the endpoints of severe AEs, discontinuation due to AEs and for various specific AEs respectively.

Overall assessment

For the assessment of the additional benefit of pirtobrutinib for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have previously been treated with a Bruton's tyrosine kinase inhibitor (BTKi) and with a B-cell lymphoma-2 (BCL-2) inhibitor, results are available from the BRUIN CLL-321 study on mortality and side effects in comparison with individualised therapy with selection of idelalisib in combination with rituximab or bendamustine in combination with rituximab.

There was no significant difference between the study arms in terms of overall survival. The results on overall survival are subject to a high risk of bias, as a high percentage of patients (37%) switched from the control arm to treatment with pirtobrutinib (treatment switching). Thus, no additional benefit is determined for the endpoint overall survival with pirtobrutinib.

For the endpoint categories of morbidity and health-related quality of life, no usable data are available from the evaluations for the EORTC QLQ-C30 and EQ-5D VAS measurement instruments, as the return rates for all questionnaires, particularly in the control arm, fall early on and differ greatly between the study arms. Thus, no additional benefit is identified for the endpoint categories morbidity and health-related quality of life.

The results on side effects for the endpoints of severe AEs, discontinuation due to AEs and specific AEs each show statistically significant differences to the advantage of pirtobrutinib compared to individualised therapy with selection of idelalisib in combination with rituximab or bendamustine in combination with rituximab.

In the overall assessment, the G-BA identified a minor additional benefit of pirtobrutinib compared to the individualised therapy with selection of idelalisib in combination with rituximab or bendamustine in combination with rituximab for the treatment of patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have previously been treated with a Bruton's tyrosine kinase inhibitor (BTKi) and with a B-cell lymphoma-2 (BCL-2) inhibitor and for whom idelalisib in combination with rituximab or bendamustine in combination with rituximab is the appropriate individualised therapy.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the randomised, open-label, controlled phase III BRUIN CLL-321 study.

The risk of bias across all endpoints of the study is rated as low.

The risk of bias of the results for overall survival is rated as high. For the endpoint of therapy discontinuation due to AEs, the risk of bias is also classified as high due to the open-label study design. The risk of bias for the results of the endpoints of severe AEs and serious AEs is classified as low.

Moreover, it is unclear whether all patients in the comparator arm received adequate premedication prior to treatment with rituximab.

Furthermore, there are uncertainties regarding the transferability of the study results to the German healthcare context, as the median number of prior therapies in patients was four in the BRUIN CLL-321 study, while the present therapeutic indication includes patients from the third line of therapy onwards.

All in all, the available data are subject to uncertainties, which leads to a limitation of the reliability of data. The reliability of data for the additional benefit is classified in the category "hint".

b2) Adults with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi) and with a B-cell lymphoma-2 (BCL-2) inhibitor and for whom venetoclax + rituximab is the appropriate individualised therapy

For the sub-population of patients for whom venetoclax in combination with rituximab is the appropriate individualised therapy, no conclusions on the additional benefit can be drawn from the BRUIN CLL-321 study. In this study, only idelalisib in combination with rituximab and bendamustine in combination with rituximab were available to the principal investigators, but not venetoclax in combination with rituximab. Thus, no data are available for the assessment of the additional benefit in this sub-population.

An additional benefit of pirtobrutinib is therefore not proven for the sub-population b2).

2.1.4 Summary of the assessment

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

"Pirtobrutinib as monotherapy is indicated for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a BTK inhibitor."

In the therapeutic indication to be considered, two patient populations were differentiated:

a) Adults with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi) and not with a B-cell lymphoma-2 (BCL-2) inhibitor

and

b) Adults with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi) and with a B-cell lymphoma-2 (BCL-2) inhibitor

On patient population a)

The G-BA determined venetoclax in combination with rituximab to be the appropriate comparator therapy. The pharmaceutical company did not submit any suitable data for this patient population. An additional benefit is therefore not proven.

On patient population b)

The G-BA determined the appropriate comparator therapy to be an individualised therapy with selection of idelalisib in combination with rituximab, venetoclax in combination with rituximab or bendamustine in combination with rituximab.

For the benefit assessment, the pharmaceutical company submitted data from the BRUIN CLL-321 study comparing pirtobrutinib versus an individualised therapy with selection of idelalisib in combination with rituximab or bendamustine in combination with rituximab.

The results of the BRUIN CLL-321 study only allow conclusions to be drawn for those patients for whom treatment with idelalisib in combination with rituximab or bendamustine in combination with rituximab is the appropriate individualised therapy, but not for patients for whom venetoclax in combination with rituximab would be indicated as the appropriate individualised therapy. A subdivision into corresponding sub-populations was therefore made during the assessment of the additional benefit:

b1) Adults with relapsed or refractory chronic lymphocytic leukaemia (CLL), who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi) and with a B-cell lymphoma-2 (BCL-2) inhibitor and for whom idelalisib + rituximab or bendamustine + rituximab is the appropriate individualised therapy

For patients for whom idelalisib + rituximab or bendamustine + rituximab is the appropriate individualised therapy, the data from the BRUIN CLL-321 study submitted by the pharmaceutical company are used.

For the overall survival, these do not show any statistically significant difference 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 as well as the EQ-5D VAS questionnaires, no usable data are available due to the low return rates of the questionnaires.

With regard to side effects, there were advantages of pirtobrutinib compared to the individualised therapy for the endpoints of severe AEs, discontinuation due to AEs and in detail for specific AEs.

In the overall assessment, a minor additional benefit is identified.

The reliability of data of the additional benefit identified is classified in the "hint" category.

b2) Adults with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi) and with a B-cell lymphoma-2 (BCL-2) inhibitor and for whom venetoclax + rituximab is the appropriate individualised therapy

No data are available from the BRUIN CLL-321 study for patients for whom venetoclax + rituximab is the appropriate individualised therapy. The additional benefit is therefore not proven for this sub-population.

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 dossier submitted by the pharmaceutical company includes an overestimation of the baseline incidence of patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a BTK inhibitor.

In order to ensure a consistent determination of the patient numbers in the present therapeutic indication, the G-BA refers to the derivation of the target population used as a basis in the resolution on the benefit assessment of zanubrutinib (resolution of 15 June 2023). A more valid estimate of the number of patients in the SHI target population is available here; this can be used despite continuing 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 Jaypirca (active ingredient: pirtobrutinib) at the following publicly accessible link (last access: 23 September 2025):

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

Treatment with pirtobrutinib should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with chronic lymphocytic leukaemia.

This medicinal product received a conditional marketing authorisation. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 August 2025). The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

The annual treatment costs shown refer to the first year of treatment.

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

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

The publications by Fischer K. et al.[4] and Furman et al.[5] were used for cost representation of bendamustine in combination with rituximab and idelalisib in combination with rituximab due to the lack of 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.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Pirtobrutinib	Continuously, 1 x daily	365.0	1	365.0
Appropriate comparator therapy				
a) Adults with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi) and not with a B-cell lymphoma-2 (BCL-2) inhibitor				
Venetoclax in combination with rituximab				

[4] Fischer, K., Cramer, P., Busch, R., Böttcher, S., Bahlo, J., Schubert, J., ... & Wendtner, C. M. (2012). Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicentre phase II trial of the German Chronic Lymphocytic Leukaemia Study Group. *Journal of Clinical Oncology*, *30*(26), 3209-3216.

[5] Furman, R. R., Sharman, J. P., Coutre, S. E., Cheson, B. D., Pagel, J. M., Hillmen, P., ... & O'Brien, S. M. (2014). Idelalisib and rituximab in relapsed chronic lymphocytic leukaemia. *New England Journal of Medicine*, *370*(11), 997-1007.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Venetoclax	Continuously, 1 x daily	365.0	1	365.0
Rituximab	Day 1 of a 28-day cycle	11.8	1	11.8
b) Adults with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi) and with a B-cell lymphoma-2 (BCL-2) inhibitor				
Idelalisib in combination with rituximab[5]				
Idelalisib	Continuously, 2 x daily	365.0	1	365.0
Rituximab	Cycle 1-5: Day 1 of a 14-day cycle Cycle 6 onwards: Day 1 of a 28-day cycle	15.0	1	15.0
Venetoclax in combination with rituximab				
Venetoclax	Continuously, 1 x daily	365.0	1	365.0
Rituximab	Day 1 of a 28-day cycle	11.8	1	11.8
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

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1,72 m; average body weight: 77.7 kg). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916)[6].

[6] Federal health reporting. Average body measurements of the population (2021, both sexes, 18 years and older), www.gbe-bund.de

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					
Pirtobrutinib	200 mg	200 mg	2 x 100 mg	365.0	730 x 100 mg
Appropriate comparator therapy					
a) Adults with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi) and not with a B-cell lymphoma-2 (BCL-2) inhibitor					
Venetoclax in combination with rituximab					
Venetoclax	Week 1: 20 mg Week 2: 50 mg Week 3: 100 mg Week 4: 200 mg Week 5 onwards: 400 mg	Week 1: 20 mg Week 2: 50 mg Week 3: 100 mg Week 4: 200 mg Week 5 onwards: 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 onwards: 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 = 716.3 mg Cycle 2 onwards: 500 mg/m^2 = 955 mg	Cycle 1: 716.3 mg Cycle 2 onwards: 955 mg	Cycle 1: 3 x 100 mg + 1 x 500 mg Cycle 2 onwards: 2 x 500 mg	11.8	3 x 100 mg + 22.6 x 500 mg
b) Adults with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi) and with a B-cell lymphoma-2 (BCL-2) 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 = 716.3 mg	Cycle 1: 716.3 mg	Cycle 1: 3 x 100 mg + 1 x 500 mg	15.0	3 x 100 mg + 29 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 onwards: 500 mg/m² = 955 mg	Cycle 2 onwards: 955 mg	Cycle 2 onwards: 2 x 500 mg		
Venetoclax in combination with rituximab					
Venetoclax	Week 1: 20 mg Week 2: 50 mg Week 3: 100 mg Week 4: 200 mg Week 5 onwards: 400 mg	Week 1: 20 mg Week 2: 50 mg Week 3: 100 mg Week 4: 200 mg Week 5 onwards: 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 onwards: 4 x 100 mg	365.0	14 x 10 mg + 7 x 50 mg + 1,369 x 100 mg
Rituximab	Cycle 1: 375 mg/m² = 716.3 mg Cycle 2 onwards: 500 mg/m² = 955 mg	Cycle 1: 716.3 mg Cycle 2 onwards: 955 mg	Cycle 1: 3 x 100 mg + 1 x 500 mg Cycle 2 onwards: 2 x 500 mg	11.8	3 x 100 mg + 22.6 x 500 mg
Bendamustine in combination with rituximab (BR)[7]					
Bendamustine	90 mg/m² = 171.9 mg	171.9 mg	1 x 100 mg + 3 x 25 mg	12.0	12 x 100 mg + 36 x 25 mg
Rituximab	Cycle 1: 375 mg/m² = 716.3 mg Cycle 2 - 6: 500 mg/m² = 955 mg	Cycle 1: 716.3 mg Cycle 2 - 6: 955 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

[7] Flinn, I. W., Van Der Jagt, R., Kahl, B. S., Wood, P., Hawkins, T. E., MacDonald, D., ... & Burke, J. M. (2014). Randomised trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. *Blood, The Journal of the American Society of Hematology*, *123*(19), 2944-2952.

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. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

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					
Pirtobrutinib	168 FCT	€ 34,990.11	€ 1.77	€ 1,995.00	€ 32,993.34
Appropriate comparator therapy					
Bendamustine 25 mg	1 PIC	€ 101.23	€ 1.77	€ 11.38	€ 88.08
Bendamustine 25 mg	5 PIC	€ 422.90	€ 1.77	€ 52.08	€ 369.05
Bendamustine 100 mg	1 PIC	€ 337.73	€ 1.77	€ 41.31	€ 294.65
Bendamustine 100 mg	5 PIC	€ 1,653.78	€ 1.77	€ 208.35	€ 1,443.66
Idelalisib 150 mg	60 FCT	€ 4,535.08	€ 1.77	€ 255.71	€ 4,277.60
Rituximab 100 mg	2 CIS	€ 717.21	€ 1.77	€ 39.08	€ 676.36
Rituximab 500 mg	1 CIS	€ 1,777.34	€ 1.77	€ 98.21	€ 1,677.36
Venetoclax 10 mg	14 FCT	€ 86.99	€ 1.77	€ 0.00	€ 85.22
Venetoclax 50 mg	7 FCT	€ 200.49	€ 1.77	€ 0.00	€ 198.72
Venetoclax 100 mg	360 FCT	€ 18,921.18	€ 1.77	€ 0.00	€ 18,919.41
Abbreviations: FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution; PIC = powder for the preparation of an infusion solution concentrate					

LAUER-TAXE® last revised: 1 August 2025

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 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:							
a) Adults with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi) and not with a B-cell lymphoma-2 (BCL-2) inhibitor							
Venetoclax in combination with rituximab							
Dimetindene IV (1 mg/10 kg, IV)	5 SFI each 4 mg	€ 26.24	€ 1.77	€ 6.92	€ 17.55	11.8	€ 82.84
Paracetamol[8] (1,000 mg, PO)	10 TAB each 1,000 mg	€ 3.32	€ 0.17	€ 0.14	€ 3.01	11.8	€ 3.55
b) Adults with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi) and with a B-cell lymphoma-2 (BCL-2) inhibitor							
Idelalisib in combination with rituximab							
Dimetindene IV (1 mg/10 kg, IV)	5 SFI each 4 mg	€ 26.24	€ 1.77	€ 6.92	€ 17.55	15.0	€ 105.30
Paracetamol[8] (1,000 mg, PO)	10 TAB each 1,000 mg	€ 3.32	€ 0.17	€ 0.14	€ 3.01	15.0	€ 4.52
Venetoclax in combination with rituximab							
Dimetindene IV (1 mg/10 kg, IV)	5 SFI each 4 mg	€ 26.24	€ 1.77	€ 6.92	€ 17.55	11.8	€ 82.84

[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	11.8	€ 3.55
Bendamustine in combination with rituximab [BR]							
Dimetindene IV (1 mg/10 kg, IV)	5 SFI each 4 mg	€ 26.24	€ 1.77	€ 6.92	€ 17.55	6.0	€ 52.65
Paracetamol[8] (1,000 mg, PO)	10 TAB each 1,000 mg	€ 3.32	€ 0.17	€ 0.14	€ 3.01	6.0	€ 3.01

Hepatitis B diagnostics

Diagnostics to rule out chronic hepatitis B requires sensibly coordinated steps. A step-by-step serological diagnosis initially consists of the examination of HBs antigen and anti-HBc antibodies. If both are negative, a past HBV infection can be excluded. In certain case constellations, further steps may be necessary in accordance with current guideline recommendations.[9]

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
HBV screening							
HBV test Hepatitis B surface antigen status (GOP 32781)	-	-	-	-	€ 5.06	1.0	€ 5.06
Anti-HBc antibody (GOP 32614)	-	-	-	-	€ 5.43	1.0	€ 5.43

[9] S3 guideline on prevention, diagnosis and therapy of hepatitis B virus infection; AWMF registry no.: 021/011 https://register.awmf.org/assets/guidelines/021-011l_S3_Prophylaxe-Diagnostik-Therapie-der-Hepatitis-B-Virusinfektion_2021-07.pdf

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 1 October 2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA have decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected

at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA have decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

a) Adults with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi) and not with a B-cell lymphoma-2 (BCL-2) inhibitor

No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

b) Adults with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a Bruton's tyrosine kinase inhibitor (BTKi) and with a B-cell lymphoma-2 (BCL-2) inhibitor

No designation of medicinal products with new active ingredients that can be used in combination therapy pursuant to Section 35a, paragraph 3, sentence 4 SGB V, as the active ingredient to be assessed is an active ingredient authorised in monotherapy.

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 their session on 7 December 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at their session on 23 April 2025.

On 10 April 2025 the pharmaceutical company submitted a dossier for the benefit assessment of pirtobrutinib to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 10 April 2025 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 pirtobrutinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 10 July 2025, and the written statement procedure was initiated with publication on the G-BA website on 15 July 2025. The deadline for submitting written statements was 5 August 2025.

The oral hearing was held on 25 August 2025.

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 26 August 2025, and the proposed draft resolution was approved.

At their session on 2 October 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	7 December 2021	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	23 April 2025	New determination of the appropriate comparator therapy
Working group Section 35a	19 August 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	25 August 2025	Conduct of the oral hearing
Working group Section 35a	3 September 2025 17 September 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	23 September 2025	Concluding discussion of the draft resolution
Plenum	2 October 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 2 October 2025

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

Prof. Hecken