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 and Annex XIIa – Combinations of Medicinal Products with New Active Ingredients according to Section 35a SGB V

Acalabrutinib

(new therapeutic indication: chronic lymphocytic leukaemia, first-line, combination with venetoclax)

of 18 December 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 pass a resolution 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 acalabrutinib (Calquence) was listed for the first time on 1 December 2020 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 2 June 2025, acalabrutinib received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 27 June 2025, i.e. at the latest within four weeks of informing the pharmaceutical company about the approval for a new therapeutic indication, 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 acalabrutinib with the new therapeutic indication

"Calquence in combination with venetoclax with or without obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)."

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 October 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 acalabrutinib 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 of 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 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 acalabrutinib.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA have made 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 Acalabrutinib (Calquence) in accordance with the product information

Calquence in combination with venetoclax with or without obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

Therapeutic indication of the resolution (resolution of 18.12.2025):

Calquence in combination with venetoclax is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

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

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with previously untreated chronic lymphocytic leukaemia (CLL)

Appropriate comparator therapy for acalabrutinib in combination with venetoclax:

– Ibrutinib ± obinutuzumab

or

– venetoclax in combination with obinutuzumab

or

– venetoclax in combination with ibrutinib

or

– acalabrutinib ± obinutuzumab

or

– zanubrutinib

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 they determine 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. The cytostatic agents bendamustine, chlorambucil and fludarabine; the B-cell receptor inhibitors ibrutinib, zanubrutinib, acalabrutinib 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 leukaemia 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 as monotherapy and in combination with obinutuzumab (resolutions of 3 June 2021)
- Ibrutinib (resolutions of 20 July 2023, 1 April 2021, 20 February 2020, 15 December 2016 and 21 July 2016)
- Idelalisib (resolution of 16 March 2017)
- Obinutuzumab (resolution of 4 November 2021)
- Venetoclax (resolutions of 15 October 2020 and 16 May 2019)
- Zanubrutinib (resolution of 15 June 2023)

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.

When determining the appropriate comparator therapy, it is assumed for the present therapeutic indication that it concerns patients requiring treatment (e.g. stage C Binet). Furthermore, it is assumed for the present therapeutic indication that an allogeneic stem cell transplantation is not indicated at the time of therapy.

According to the present guidelines and the written statement of the Drugs Commission of the German Medical Association (AkdÄ), a therapy based on a Bruton Tyrosine Kinase (BTK) inhibitor is recommended for patients with previously untreated CLL. In this regard, the BTK inhibitors acalabrutinib as monotherapy or in combination with obinutuzumab, ibrutinib as monotherapy or in combination with rituximab or obinutuzumab or in combination with venetoclax and zanubrutinib as monotherapy are approved.

The combination therapy ibrutinib and rituximab is not explicitly recommended in the written statement of the AkdÄ. The present guidelines state that no advantage of this combination therapy over monotherapy with ibrutinib could be shown on the basis of study data. Therefore, the G-BA did not determine ibrutinib + rituximab as an appropriate comparator therapy.

Overall, the following BTK inhibitors or combination therapies with BTK inhibitors are therefore determined as appropriate comparator therapies: Ibrutinib, ibrutinib + obinutuzumab, acalabrutinib, acalabrutinib + obinutuzumab and zanubrutinib.

In addition to BTK inhibitor-based therapy, the present guidelines also recommend the use of the BCL-2 inhibitor venetoclax for the first-line treatment of CLL. In line with the written statement of the AkdÄ, the therapy options venetoclax in combination with obinutuzumab or venetoclax in combination with ibrutinib are specifically recommended.

By resolution of 15 October 2020, no additional benefit of venetoclax in combination with obinutuzumab compared with the corresponding comparator therapies was identified for the sub-populations investigated in each case, as no appropriate data to demonstrate the additional benefit were presented.

No additional benefit of the combination therapy ibrutinib + venetoclax over chlorambucil + obinutuzumab was identified based on data in the patient group of adults without genetic risk factors who are not eligible for therapy with FCR due to their general condition and comorbidities (resolution of 20 July 2023).

Combination therapies consistently assume high significance in the present guidelines and the written statement of the AkdÄ. Overall, it is considered appropriate to determine venetoclax + obinutuzumab and venetoclax + ibrutinib as appropriate comparator therapies.

The available guidelines and the written statement of the AkdÄ unanimously state that the use of chemoimmunotherapies FCR, bendamustine in combination with rituximab (BR) and chlorambucil in combination with obinutuzumab (ClbO) is only recommended in exceptional cases. The written statement of the AkdÄ explicitly mentions the significantly shorter progression-free survival compared to chemotherapy-free treatments.

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

Overall, the chemoimmunotherapies FCR, BR, ClbR or ClbO are not determined as the appropriate comparator therapy.

The appropriate comparator therapy determined here includes several therapeutic alternatives. These therapeutic alternatives are equally appropriate for the comparator therapy.

The additional benefit can be demonstrated compared to one of the therapeutic alternatives mentioned.

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 acalabrutinib is assessed as follows:

An additional benefit is not proven.

Justification:

The pharmaceutical company presented the results of the AMPLIFY study for the proof of an additional benefit of acalabrutinib in combination with venetoclax for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia.

The AMPLIFY study is an open-label, multicentre, randomised, controlled phase III study, which has been ongoing since February 2019 and compared acalabrutinib + venetoclax (AV) or acalabrutinib + venetoclax + obinutuzumab (AVO) with chemoimmunotherapy (either fludarabine + cyclophosphamide + rituximab or bendamustine + rituximab).

The study was conducted in 133 study sites across 27 countries in Europe, Asia, North and South America, South Africa and Australia.

Adult patients with previously untreated CLL without the presence of a deletion in the short arm of chromosome 17 (17p deletion) or a mutation of the tumour protein p53 (TP53 mutation) were enrolled in the study. A total of 867 patients were enrolled in the study and randomised in a 1:1:1 ratio to the study arms (N=291 AV-arm; N=286 AVO-arm; N=290 FCR/BR-arm). Randomisation was stratified by age (<65 or ≥65 years), IGHV mutational status (mutated vs unmutated), Rai status (high risk [≥3] vs no high risk [<3]) and geographical region (North America vs Europe vs other).

Overall, two data cut-offs are available:

− 1st data cut-off from 30.04.2024: interim analysis

− 2nd data cut-off from 30.10.2024: FDA-required data cut-off

Conclusion

The chemoimmunotherapies (fludarabine + cyclophosphamide + rituximab or bendamustine + rituximab) used in the comparator arm of the AMPLIFY study do not correspond to the appropriate comparator therapy determined by the G-BA. The AMPLIFY study submitted by the pharmaceutical company is therefore not suitable for demonstrating the additional benefit of acalabrutinib in combination with venetoclax. An additional benefit of acalabrutinib in combination with venetoclax for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia is therefore not proven.

2.1.4 Summary of the assessment

The present benefit assessment is the benefit assessment of a new therapeutic indication for the active ingredient acalabrutinib:

"Calquence in combination with venetoclax with or without obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)."

The present benefit assessment relates to acalabrutinib in combination with venetoclax.

As the appropriate comparator therapy, the G-BA determined the following monotherapies and combination therapies as therapeutic alternatives: Ibrutinib ± obinutuzumab, venetoclax in combination with obinutuzumab, venetoclax in combination with ibrutinib, acalabrutinib ± obinutuzumab and zanubrutinib.

The chemoimmunotherapies (fludarabine + cyclophosphamide + rituximab or bendamustine + rituximab) used in the comparator arm of the AMPLIFY study do not correspond to the appropriate comparator therapy. No suitable data are therefore available for the benefit assessment of acalabrutinib in combination with venetoclax versus the appropriate comparator therapy.

An additional benefit is therefore not proven.

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

The information on the number of patients is based on the target population in statutory health insurance (SHI).

As part of the written statement procedure, the pharmaceutical company presented additional information on the calculation of the number of patients in the SHI target population as well as a new lower limit for the SHI target population.

The pharmaceutical company considered the data from the associated dossier (approx. 3,200 patients) to be the upper limit. The new lower limit is based on an individual request for data from the German Centre for Cancer Registry Data (ZfKD) at the Robert Koch Institute (RKI) and refers to the clinical data record of the ZfKD (last revised: 24.06.2025), which is available from the diagnosis year 2020 and includes information on the course of the disease and detailed information on therapy (tumour-related operations, radiotherapy, systemic therapy).

This procedure is mathematically comprehensible and methodologically appropriate in principle. However, there are uncertainties regarding the incidence of CLL, particularly due to the time lapse between initial diagnosis and first-line CLL treatment. There is also a lack of information on the criteria used by the pharmaceutical company to select the patients with first-line treatment in the data record. In addition, the ZfKD assumes that not all therapies and progression events have been reported to the cancer registry despite the obligation to report.

Against this background, the lower limit newly presented by the pharmaceutical entrepreneur must be regarded as underestimated. Based on the sources submitted in 2014, the upper limit is in a largely plausible range and is therefore consistent with the most recent resolutions in the present therapeutic indication (ibrutinib by resolution of 20 July 2023).

Overall, the number of approximately 3,200 patients presented with the dossier is considered to be in a plausible range.

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 Calquence (active ingredient: acalabrutinib) at the following publicly accessible link (last access: 12 December 2025):

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

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

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 October 2025). The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

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 is different 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.

Adults with previously untreated chronic lymphocytic leukaemia (CLL)

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Acalabrutinib in combination with venetoclax				
1st year (cycle 1-13)[2]				
Acalabrutinib	Continuously, 2 x daily	365	1	365
Venetoclax	Cycle 3: 1 x daily for 7 days each in 4 dosage steps Cycle 4–13: 1 x daily	309	1	309
2nd year (cycle 14)				
Acalabrutinib	2 x daily	27	1	27
Venetoclax	1 x daily	27	1	27
Appropriate comparator therapy				
Ibrutinib monotherapy				
1st year and subsequent years				
Ibrutinib	Continuously, 1 x daily	365	1	365
Ibrutinib in combination with obinutuzumab				
1st year				
Ibrutinib	Continuously, 1 x daily	365	1	365

[2] A cycle comprises 28 days.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Obinutuzumab	Every 28 days on day 1, 8, 15 of cycle 1 and on day 1 of cycle 2-6[3]	6	Cycle 1: 3 Cycle 2–6: 1	8
Subsequent years				
Ibrutinib	Continuously, 1 x daily	365	1	365
Venetoclax in combination with obinutuzumab				
1st year[4]				
Venetoclax	Cycle 1–2: On day 22 in cycle 1 until day 28 in cycle 2, 1 x daily for 7 days each in 4 dosage steps Cycle 3–12: 1 x daily	315	1	315
Obinutuzumab	Every 28 days on day 1, 8, 15 of cycle 1 and on day 1 of cycle 2-6[3]	6	Cycle 1: 3 Cycle 2–6: 1	8
Venetoclax in combination with ibrutinib				
1st year (cycle 1-13)				
Venetoclax	Cycle 4: 1 x daily for 7 days each in 4 dosage steps Cycle 5–13: 1 x daily	281	1	281
Ibrutinib	Continuously, 1 x daily	365	1	365
2nd year (cycle 14-15)				
Venetoclax	Cycle 14-15 1 x daily	55	1	55

[3] The first dose of obinutuzumab was divided between day 1 (100 mg) and day 2 (900 mg).
[4] As treatment with venetoclax is limited to a total of 12 cycles, the costs are only incurred in the 1st year of treatment.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Ibrutinib	1 x daily	55	1	55
Acalabrutinib monotherapy				
1st year and subsequent years				
Acalabrutinib	Continuously, 2 x daily	365	1	365
Acalabrutinib in combination with obinutuzumab				
1st year				
Acalabrutinib	Continuously, 2 x daily	365	1	365
Obinutuzumab	Every 28 days on day 1, 8, 15 of cycle 2 and on day 1 of cycle 3-7[3]	6	Cycle 2: 3 Cycle 3–7: 1	8
Subsequent years				
Acalabrutinib	Continuously, 2 x daily	365	1	365
Zanubrutinib monotherapy				
1st year and subsequent years				
Zanubrutinib	Continuously, 1 x daily	365	1	365

Consumption:

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

Adults with previously untreated chronic lymphocytic leukaemia (CLL)

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					
Acalabrutinib in combination with venetoclax					
1st year (cycle 1-13)					
Acalabrutinib	100 mg	200 mg	2 x 100 mg	365.0	730 x 100 mg
Venetoclax	Cycle 3 20 mg 50 mg 100 mg 200 mg	 20 mg 50 mg 100 mg 200 mg	 2 x 10 mg 1 x 50 mg 1 x 100 mg 2 x 100 mg	 7.0 7.0 7.0 7.0	 14 x 10 mg 7 x 50 mg 7 x 100 mg 14 x 100 mg
	Cycle 4-13 400 mg	400 mg	4 x 100 mg	309.0	1,124 x 100 mg
2nd year (cycle 14)					
Acalabrutinib	100 mg	200 mg	2 x 100 mg	27.0	54 x 100 mg
Venetoclax	Cycle 14 400 mg	400 mg	4 x 100 mg	27.0	108 x 100 mg
Appropriate comparator therapy					
Ibrutinib monotherapy					
1st year and subsequent years					
Ibrutinib	420 mg	420 mg	1 x 420 mg	365.0	365 x 420 mg
Ibrutinib in combination with obinutuzumab					
1st year					
Ibrutinib	420 mg	420 mg	1 x 420 mg	365.0	365 x 420 mg
Obinutuzumab	1,000 mg	1,000 mg	1 x 1,000 mg	8.0	8 x 1,000 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
Subsequent years					
Ibrutinib	420 mg	420 mg	1 x 420 mg	365.0	365 x 420 mg
Venetoclax in combination with obinutuzumab					
1st year[4]					
Venetoclax	Cycle 1-2 20 mg 50 mg 100 mg 200 mg	 20 mg 50 mg 100 mg 200 mg	 2 x 10 mg 1 x 50 mg 1 x 100 mg 2 x 100 mg	 7.0 7.0 7.0 7.0	 14 x 10 mg 7 x 50 mg 7 x 100 mg 14 x 100 mg
	Cycle 2-12 400 mg	 400 mg	 4 x 100 mg	 287.0	 1,148 x 100 mg
Obinutuzumab	1,000 mg	1,000 mg	1 x 1,000 mg	8.0	8 x 1,000 mg
Venetoclax in combination with ibrutinib					
1st year (cycle 1-13)					
Venetoclax	Cycle 4 20 mg 50 mg 100 mg 200 mg	 20 mg 50 mg 100 mg 200 mg	 2 x 10 mg 1 x 50 mg 1 x 100 mg 2 x 100 mg	 7.0 7.0 7.0 7.0	 14 x 10 mg 7 x 50 mg 7 x 100 mg 14 x 100 mg
	Cycle 5-13 400 mg	 400 mg	 4 x 100 mg	 253.0	 1,012 x 100 mg
Ibrutinib	420 mg	420 mg	1 x 420 mg	365.0	365 x 420 mg
2nd year (cycle 14-15)					
Venetoclax	Cycle 14-15 400 mg	 400 mg	 4 x 100 mg	 55.0	 220 x 100 mg
Ibrutinib	420 mg	420 mg	1 x 420 mg	55.0	55 x 420 mg
Acalabrutinib monotherapy					
1st year and subsequent years					
Acalabrutinib	100 mg	200 mg	2 x 100 mg	365.0	730 x 100 mg
Acalabrutinib in combination with obinutuzumab					
1st year					
Acalabrutinib	100 mg	200 mg	2 x 100 mg	365.0	730 x 100 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
Obinutuzumab	1,000 mg	1,000 mg	1 x 1,000 mg	8.0	8 x 1,000 mg
Subsequent years					
Acalabrutinib	100 mg	200 mg	2 x 100 mg	365.0	730 x 100 mg
Zanubrutinib monotherapy					
1st year and subsequent years					
Zanubrutinib	320 mg	320 mg	4 x 80 mg	365.0	1,460 x 80 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. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Adults with previously untreated chronic lymphocytic leukaemia (CLL)

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					
Acalabrutinib 100 mg	60 FCT	€ 6,181.12	€ 1.77	€ 0.00	€ 6,179.35
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	112 FCT	€ 5,926.31	€ 1.77	€ 0.00	€ 5,924.54
Venetoclax 100 mg	360 FCT	€ 18,921.18	€ 1.77	€ 0.00	€ 18,919.41
Appropriate comparator therapy					
Acalabrutinib 100 mg	60 FCT	€ 6,181.12	€ 1.77	€ 0.00	€ 6,179.35
Ibrutinib 420 mg	28 FCT	€ 5,767.13	€ 1.77	€ 0.00	€ 5,765.36
Obinutuzumab 1,000 mg	1 CIS	€ 2,649.25	€ 1.77	€ 148.01	€ 2,499.47
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	7 FCT	€ 389.67	€ 1.77	€ 0.00	€ 387.90
Venetoclax 100 mg	112 FCT	€ 5,926.31	€ 1.77	€ 0.00	€ 5,924.54
Venetoclax 100 mg	360 FCT	€ 18,921.18	€ 1.77	€ 0.00	€ 18,919.41
Zanubrutinib 80 mg	120 HC	€ 5,479.32	€ 1.77	€ 0.00	€ 5,477.55
Abbreviations: FCT = film-coated tablets; HC = hard capsules; CIS = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 15 October 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.

The calculation of the additionally required SHI services is based on packs in distribution with the LAUER-TAXE® last revised on 15 September 2025 and fee structure items (FSI) - last revised in the 3rd quarter of 2025 - of the uniform value scale (UVS 2025/Q3).

Premedication for prevention

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

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 obinutuzumab							
Dimetindene IV (1 mg/10 kg, IV)	5 SFI	€ 26.24	€ 1.77	€ 6.92	€ 17.55	6.0	€ 52.65
Paracetamol[5] (1,000 mg, PO)	10 TAB	€ 3.32	€ 0.17	€ 0.14	€ 3.01	6.0	€ 3.01
Dexamethasone[5] (5 x 4 mg IV)	10 SFI	€ 16.92	€ 1.77	€ 0.36	€ 14.79	12.0	€ 88.74
Venetoclax in combination with obinutuzumab							
Dimetindene IV (1 mg/10 kg, IV)	5 SFI	€ 26.24	€ 1.77	€ 6.92	€ 17.55	6.0	€ 52.65
Paracetamol[5] (1,000 mg, PO)	10 TAB	€ 3.32	€ 0.17	€ 0.14	€ 3.01	6.0	€ 3.01
Dexamethasone[5] (5 x 4 mg IV)	10 SFI	€ 16.92	€ 1.77	€ 0.36	€ 14.79	12.0	€ 88.74
Acalabrutinib in combination with obinutuzumab							
Dimetindene IV (1 mg/10 kg, IV)	5 SFI	€ 26.24	€ 1.77	€ 6.92	€ 17.55	6.0	€ 52.65
Paracetamol[5] (1,000 mg, PO)	10 TAB	€ 3.32	€ 0.17	€ 0.14	€ 3.01	6.0	€ 3.01
Dexamethasone[5] (5 x 4 mg IV)	10 SFI	€ 16.92	€ 1.77	€ 0.36	€ 14.79	12.0	€ 88.74

Hepatitis B diagnostics

Patients should be tested for HBV infection before starting treatment.

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

[5] Fixed reimbursement rate

constellations, further steps may be necessary in accordance with current guideline recommendations.[6]

The costs of HBV testing are not presented as there is no regular difference between the medicinal product to be assessed and the appropriate comparator therapy.

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

[6] 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

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 have 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:

Adults with previously untreated chronic lymphocytic leukaemia (CLL)

Each of the designated medicinal products is an active ingredient that is specifically named as a concomitant active ingredient in the product information for the assessed medicinal product. Corresponding text extract from the product information for the assessed medicinal product: "Calquence in combination with venetoclax with or without obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)".

For the designated medicinal products, the requirements of Section 35a, paragraph 3, sentence 4 SGB V are also fulfilled.

References:
Product information for acalabrutinib (Calquence); Calquence® 100 mg film-coated tablets; last revised: July 2025

Supplement to Annex XIIa of the Pharmaceuticals Directive

Since the resolution under I.5 mentions medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V, which can be used in a combination therapy with the assessed active ingredient in the therapeutic indication of the resolution, the information on this designation is to be added to Annex XIIa of the Pharmaceuticals Directive and provided with patient-group-related information on the period of validity of the designation.

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 6 May 2025, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 27 June 2025 the pharmaceutical company submitted a dossier for the benefit assessment of acalabrutinib to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 1 July 2025 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 acalabrutinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 September 2025, and the written statement procedure was initiated with publication on the G-BA website on 1 October 2025. The deadline for submitting statements was 22 October 2025.

The oral hearing was held on 10 November 2025.

By letter dated 11 November 2025, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 27 November 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 9 December 2025, and the proposed draft resolution was approved.

At their session on 18 December 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	6 May 2025	Determination of the appropriate comparator therapy
Working group Section 35a	5 November 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	10 November 2025; 11 November 2025	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents

Working group Section 35a	19 November 2025; 3 December 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	9 December 2025	Concluding discussion of the draft resolution
Plenum	18 December 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 18 December 2025

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

Prof. Hecken