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
Acalabrutinib (new therapeutic indication: mantle cell lymphoma, not eligible for autologous stem cell transplant, first-line, combination with bendamustine and rituximab)

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 14 February 2025, the pharmaceutical company submitted an application for postponement of the date for the start of the benefit assessment procedure for acalabrutinib in the therapeutic indication "Combination with bendamustine and rituximab (BR) for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are not eligible for autologous stem cell transplant (ASCT)" in accordance with Section 35a paragraph 5b SGB V.

The pharmaceutical company expected extensions of the marketing authorisation for the active ingredient acalabrutinib within the period specified in Section 35a paragraph 5b SGB V for multiple therapeutic indications at different times.

At their session on 3 April 2025, the G-BA approved the application pursuant to Section 35a paragraph 5b SGB V and postponed the relevant date for the start of the benefit assessment and the submission of a dossier for the benefit assessment for the therapeutic indication in question to four weeks after the marketing authorisation of the other therapeutic indication of the therapeutic indication covered by the application, at the latest six months after the first relevant date. The marketing authorisation for the other therapeutic indication covered by the application according to Section 35a paragraph 5b SGB V was granted within the 6-month period.

On 2 May 2025, acalabrutinib received extension of the marketing authorisation for the therapeutic indications "In combination with bendamustine and rituximab (BR) for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are not eligible for autologous stem cell transplant (ASCT)" and "Monotherapy for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have not previously been treated with a BTK inhibitor". The extensions of the marketing authorisation for the therapeutic indications "Chronic lymphocytic leukaemia, first-line, combination with venetoclax" and "Chronic lymphocytic leukaemia, first-line, combination with venetoclax and obinutuzumab" were granted on 2 June 2025. The mentioned extensions of the marketing authorisation are 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, the pharmaceutical company submitted a dossier in due time in accordance with Section 4, paragraph 3, No. 3 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 2 of the Rules of Procedure of the G-BA (VerfO) for the active ingredient acalabrutinib with the therapeutic indication "Calquence in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are not eligible for autologous stem cell transplant (ASCT)".

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), therefore 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 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 bendamustine and rituximab (BR) is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are not eligible for autologous stem cell transplant (ASCT).

Therapeutic indication of the resolution (resolution of 18.12.2025):

See the approved therapeutic indication.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant

Appropriate comparator therapy for acalabrutinib in combination with BR:

– Individualised therapy with selection of

- Rituximab in combination with CHOP (cyclophosphamide in combination with doxorubicin, vincristine, predniso(lo)ne) [see Annex VI, XXVI. Rituximab for mantle cell lymphoma],
- VR-CAP (bortezomib in combination with rituximab, cyclophosphamide, doxorubicin, prednisone) and
- BR (bendamustine in combination with rituximab)

if complete or partial remission is achieved after induction therapy with R-CHOP or BR followed by

- maintenance treatment with rituximab

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.

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

On 1. Bortezomib and ibrutinib are explicitly approved for the treatment of previously untreated mantle cell lymphoma. Mantle cell lymphoma is a type of non-Hodgkin lymphoma. Accordingly, the cytostatic agents bleomycin, chlorambucil, cyclophosphamide, cytarabine, doxorubicin, etoposide, methotrexate, mitoxantrone, vinblastine, vincristine and vindesine as well as the glucocorticoids dexamethasone, prednisone and prednisolone have also been granted a marketing authorisation.

On 2. A radiotherapy is considered as a non-medicinal treatment in the present therapeutic indication.

On 3. A resolution of the G-BA on Annex VI to Section K of the Pharmaceuticals Directive - Prescribability of approved medicinal products in non-approved therapeutic indications (so-called off-label use) is available:

- Rituximab in mantle cell lymphoma

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

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

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

In the present therapeutic indication, it is assumed that the patients have an indication for systemic antineoplastic therapy due to a correspondingly extensive-stage of the disease, in particular with regard to a symptomatic course, and therefore, among other things, a watch-and-wait strategy is not considered.

Furthermore, it is assumed that the patient population according to the therapeutic indication does not include patients with poor or reduced general condition and that there is no indication for radiotherapy at the time of treatment.

According to the available guidelines and the written statement of the AkdÄ and the DGHO, chemoimmunotherapy with R-CHOP, VR-CAP or BR is unanimously recommended for adults with untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant. The choice of specific chemoimmunotherapy is made on an individual basis. With regard to the selection of therapy options, the AkdÄ stated that the general condition, age, relevant comorbidities and the toxicity profile of the respective therapy option should be taken into account when making the treatment decision.

VR-CAP is approved for the present therapeutic indication. Induction therapy with R-CHOP can be prescribed for off-label use in accordance with Annex VI of the Pharmaceuticals Directive.

Treatment with BR is not approved for the present indication. Data on BR versus R-CHOP are available from randomised studies in the present indication.[1,2]

In accordance with the generally recognised state of medical knowledge, it must be established in the overall assessment that the off-label use of BR for relevant patient groups or indication areas is considered the therapy standard in the therapeutic indication to be assessed and is generally preferable to the medicinal products

[1] Flinn IW, van der Jagt R, Kahl B, et al. First-Line Treatment of Patients With Indolent Non-Hodgkin Lymphoma or Mantle-Cell Lymphoma With Bendamustine Plus Rituximab Versus R-CHOP or R-CVP: Results of the BRIGHT 5-Year Follow-Up Study. *J Clin Oncol*. 2019;37(12):984-991.

[2] Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013;381(9873):1203-1210.

previously approved in the therapeutic indication; Section 6, paragraph 2, sentence 3, number 3 AM-NutzenV.

The active ingredient ibrutinib is a new treatment option in the present therapeutic indication. The active ingredient was recently approved (marketing authorisation on 18 July 2025) in combination with R-CHOP alternating with R-DHAP (or R-DHAOx; rituximab, dexamethasone, cytarabine, cisplatin or oxaliplatin) without ibrutinib, followed by ibrutinib as monotherapy, for the treatment of adults with previously untreated mantle cell lymphoma who may be eligible for autologous stem cell transplant. Based on this formulation, it cannot be ruled out that ibrutinib in the combination therapy mentioned does not also represent a potential therapy option for adults without eligibility for autologous stem cell transplant. Based on the generally accepted state of medical knowledge, ibrutinib is not determined to be an appropriate comparator therapy for the present resolution.

In addition, the available evidence also recommends lenalidomide in combination with rituximab and the chemoimmunotherapy R-BAC (rituximab + bendamustine + cytarabine). Lenalidomide in combination with rituximab is not approved for the therapeutic indication of newly diagnosed mantle cell lymphoma and the available evidence does not indicate its preference over approved therapy options. Lenalidomide in combination with dexamethasone is therefore not determined to be an appropriate comparator therapy. According to the DGHO's written statement, R-BAC may only come into question in very fit patients with a high risk profile, which is why R-BAC is not considered a regularly used treatment option in the present therapeutic indication and is therefore not included in the appropriate comparator therapy.

<u>On maintenance treatment:</u>

According to the present guidelines, maintenance treatment with rituximab is recommended after therapy with R-CHOP and BR. The off-label use of rituximab following treatment with R-CHOP can be prescribed in accordance with Annex VI of the Pharmaceuticals Directive. With regard to maintenance treatment with rituximab, the specifications in Annex VI of the Pharmaceuticals Directive must be taken into account for subjects who have undergone prior R-CHOP therapy. Maintenance treatment with rituximab following induction therapy is not approved. Dosage and treatment regimen should correspond to the generally recognised state of medical knowledge.

Rituximab is not approved for use after therapy with BR. For the use of rituximab as maintenance treatment following induction therapy with BR, these guidelines refer to a randomised phase II study and a retrospective cohort study.[3,4]

In accordance with the generally recognised state of medical knowledge, it must be established in the overall assessment that the off-label use of maintenance treatment with rituximab for relevant patient groups or indication areas is considered the therapy standard in the therapeutic indication to be assessed and is generally preferable to the

[3] Mathias J. Rummel et al. Two years rituximab maintenance vs. observation after first-line treatment with bendamustine plus rituximab (B-R) in patients with mantle cell lymphoma: First results of a prospective, randomized, multicenter phase II study (a subgroup study of the StiL NHL7-2008 MAINTAIN trial). JCO 34, 7503-7503(2016)

[4] Martin P, Cohen JB, Wang M, et al. Treatment Outcomes and Roles of Transplantation and Maintenance Rituximab in Patients With Previously Untreated Mantle Cell Lymphoma: Results From Large Real-World Cohorts. J Clin Oncol. 2023;41(3):541-554.

medicinal products previously approved in the therapeutic indication; Section 6, paragraph 2, sentence 3, number 3 AM-NutzenV.

In the overall assessment, the G-BA determine the appropriate comparator therapy to be an individualised therapy with selection of R-CHOP, BR and VR-CAP, followed by maintenance treatment with rituximab if a complete or partial remission is achieved after chemoimmunotherapy with R-CHOP or BR.

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

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:

a) Adults with untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant

a1) Adults with untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant and for whom bendamustine in combination with rituximab is an appropriate individualised therapy

An additional benefit is not proven.

a2) Adults with untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant and for whom bendamustine in combination with rituximab is not an appropriate individualised therapy

An additional benefit is not proven.

Justification:

The pharmaceutical company presented results from the pivotal phase III ECHO study for the benefit assessment of acalabrutinib in combination with BR for the treatment of adults with previously untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant.

The ongoing ECHO study is a double-blind, randomised controlled trial comparing acalabrutinib in combination with BR versus placebo in combination with BR in adults with previously untreated mantle cell lymphoma. An approximation of unsuitability for autologous stem cell transplant is represented by the age of at least 65 years at the time of enrolment in the study, as well as by the exclusion of patients for whom tumour reduction was intended prior to stem cell transplantation.

Among others, patients with relevant cardiovascular disorders and risk of haemorrhage are excluded from the study.

The primary endpoint of the ECHO study is progression-free survival (PFS). Other endpoints include overall survival, patient-reported endpoints on morbidity and health-related quality of life as well as adverse events.

The ECHO study has been ongoing since May 2017 in a total of 189 study sites in Europe, South America, Asia, North America and Australia.

A total of 598 patients were enrolled in the analyses based on the ITT population and randomised in a 1:1 ratio to either treatment with acalabrutinib + BR (N = 299) or placebo + BR (N = 299). It was stratified by geographic region (North America vs Western Europe vs other) and the simplified Mantle cell lymphoma International Prognostic Index (MIPI) score (low risk [0-3] vs intermediate risk [4-5] vs high risk [6-11]).

Evaluations of the primary data cut-off from 15 February 2024, which represents the pre-specified interim analysis after around 250 events in the PFS endpoint, were presented. For the endpoint of overall survival, the pharmaceutical company presented additional results in the dossier for the data cut-off from 12 August 2024, which was requested by the US regulatory authority. For the present benefit assessment, the data cut-off from 12 August 2024 is used for the endpoint category of mortality and the data cut-off from 15 February 2024 is used for morbidity, health-related quality of life and side effects, as the majority of patients had already completed both the approx. 6-month induction therapy and the approx. 2-year maintenance treatment with rituximab at the first data cut-off (15 February 2024), the patients had already been observed for a median of almost 4 years (with regard to overall survival), a relevant number of patients with event for side effects have not been added at the later data cut-off (12 August 2024) and the influence of the additional surveys of patient-reported endpoints on the results is also considered to be low.

In addition, the pharmaceutical company submitted further data on therapy discontinuation due to adverse events (AEs) for the endpoint category of side effects in the written statement procedure.

<u>On the implementation of the appropriate comparator therapy:</u>

The combination therapy BR used in the comparator arm of the study is a component of the individualised therapy of the appropriate comparator therapy. This means that there is no choice of several treatment options available to the investigators in the study that would enable an individualised treatment decision. Due to the comparator selected in the ECHO study, the assessment is carried out separately for two patient groups in accordance with the suitability of BR as an individualised therapy. It is assumed that sufficiently adequate treatment of patients in patient group a1) (patients for whom bendamustine in combination with rituximab is an appropriate individualised therapy) is guaranteed despite the lack of choice in the ECHO study.

Extent and probability of the additional benefit

a1) Adults with untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant and for whom bendamustine in combination with rituximab is an appropriate individualised therapy

Mortality

Overall survival was operationalised in the ECHO study as the time from randomisation to death from any cause, regardless of whether patients discontinued randomised therapy or received subsequent therapy.

However, there were no statistically significant differences between the treatment arms for the overall survival.

The information on the subsequent therapies used after the termination of study medication shows that relatively few subsequent therapies were initiated in the intervention arm, whereas relatively many subsequent therapies with acalabrutinib were started in the comparator arm. Specifically, according to the IQWiG benefit assessment based on the interim analysis (15 February 2024), the percentage of patients in whom subsequent therapy was initiated after disease progression was around 75% in the comparator arm and only around 39% in the intervention arm. The pharmaceutical company commented on this difference in the written statement procedure that, according to the study design, subjects from the comparator arm were offered subsequent therapy with acalabrutinib (cross-over or treatment switch), whereas the reason for the low use of subsequent therapy in the intervention arm was prolonged progression-free survival (PFS) and a possible delay in reporting the first data cut-off.

From the G-BA's point of view, the unequal use of subsequent therapies between the study arms results in an increased endpoint-specific risk of bias. The interpretability of overall survival is also considered difficult in the assessment report by the European Medicines Agency (EMA) on Calquence from 27 March 2025 against the background of the treatment switch in the comparator arm.

Morbidity

Progression-free survival (PFS)

PFS is the primary endpoint of the ECHO study and is operationalised as the time from randomisation to disease progression or death from any cause, whichever event occurs first.

There was a statistically significant difference in favour of acalabrutinib + BR compared to BR.

The PFS endpoint is a composite endpoint composed of endpoints of the categories "mortality" and "morbidity". The endpoint component "mortality" has already been assessed as an independent endpoint via the endpoint "overall survival". The morbidity component "disease progression" is assessed according to the criteria for Lugano classification of non-Hodgkin lymphomas and thus, not in a symptom-related manner but 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 PFS endpoint. The overall statement on the additional benefit remains unaffected.

EORTC QLQ-C30 Symptom scales

In the ECHO study, disease symptomatology was assessed using the symptom scales of the cancer-specific EORTC-QLQ-C30 questionnaire. In the dossier, the pharmaceutical company presented responder analyses for the time to first deterioration by ≥ 10 points.

For the symptom scales of pain and diarrhoea, there was a statistically significant difference to the disadvantage of acalabrutinib + BR compared to BR.

For the remaining symptom scales, there were no statistically significant differences between the treatment arms.

Overall, there was a disadvantage for symptomatology that is considered relevant in terms of clinical significance, but is no longer considered minor in its extent.

Health status (EQ-5D VAS)

Health status was assessed in the ECHO study using the visual analogue scale (VAS) of the European Quality of Life Questionnaire 5 Dimensions (EQ-5D) and presented in the dossier as a responder analysis for the time to first deterioration by ≥ 15 points.

For the health status, there was no statistically significant difference between the study arms.

Quality of life

EORTC QLQ-C30 functional scales

In the ECHO study, health-related quality of life was assessed using the functional scales of the cancer-specific EORTC-QLQ-C30 questionnaire. In the dossier, the pharmaceutical company presented responder analyses for the time to first deterioration by ≥ 10 points.

There was no statistically significant difference between the study arms for each one of the scales of health-related quality of life of the EORTC QLQ-C30.

FACT-Lym

In addition, health-related quality of life was assessed in the ECHO study using the lymphoma-specific Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym) questionnaire. In the dossier, the pharmaceutical company presented responder analyses for the time to first deterioration by ≥ 25.2 points.

No statistically significant difference between the study arms could be observed.

Side effects

Cross-endpoint note

The pharmaceutical company presented time-time-to-event analyses for the endpoints in the category of side effects and uses the hazard ratio (HR) as an effect size. The number of patients who experienced an event was examined in the present benefit assessment since the median observation periods between the study arms are sufficiently similar in the present setting. Instead of the hazard ratio, the relative risk is thus used for the present benefit assessment.

Adverse events (AEs)

In the ECHO study, almost all study participants experienced an AE. The results are only presented additionally.

Serious AEs (SAEs) and severe AEs

For the endpoints of SAEs and severe AEs, there were no statistically significant differences between the study arms of the ECHO study.

Therapy discontinuation due to AEs

In the endpoint "Therapy discontinuation due to AEs", the ECHO study showed a statistically significant difference to the disadvantage of acalabrutinib + BR compared to BR.

The reliability of data for the endpoint "Therapy discontinuation due to AEs" is limited. This is due to the fact that premature therapy discontinuation for reasons other than AE (e.g. due to disease progression) is a competing event. This means that the "Therapy discontinuation" criterion can no longer be recorded for AEs that may still occur after discontinuation for reasons other than AEs.

In the written statement procedure, the pharmaceutical company submitted the censoring reasons for "Therapy discontinuation due to AEs".

The assessment of the reasons for censoring does not result in a different assessment of the statistically significant difference.

Specific AEs

For the endpoints "Cardiac disorders (SOC, severe AEs)", "Infections and infestations (SOC, severe AEs)" and "Severe bleeding (SMQ, severe AEs)", there was no significant difference between the study arms of the ECHO study.

The endpoint "Bleeding (SMQ, AEs)" showed a statistically significant difference to the disadvantage of acalabrutinib + BR compared to BR.

In addition, statistically significant differences to the disadvantage of acalabrutinib + BR compared to BR were observed for each of the endpoints "Vomiting (PT, AEs)", "Headache (PT, AEs)", "Skin and subcutaneous tissue disorders (SOC, severe AEs)", "Leukopenia (PT, severe AEs)" and "Hepatotoxicity (severe AEs)".

For the endpoint "Injury, poisoning and procedural complications (SOC, SAEs)", there was a statistically significant difference in favour of acalabrutinib + BR compared to BR.

Conclusion on side effects

The overall assessment did not show any statistically significant differences between the treatment arms for SAEs and severe AEs in the endpoint category of side effects. For the endpoint "Therapy discontinuations due to AEs", there was a disadvantage of the acalabrutinib combination. In detail, there were predominantly disadvantages of the acalabrutinib combination for specific AEs.

Overall, a disadvantage is derived in the endpoint category of side effects due to the disadvantage in "Therapy discontinuation due to AEs".

Overall assessment

Results on the endpoint categories of mortality, morbidity, quality of life and side effects from the ECHO study comparing acalabrutinib + BR versus BR are available for the assessment of the additional benefit of acalabrutinib in combination with bendamustine and rituximab (BR) for the treatment of adults with untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant and for whom BR is an appropriate individualised therapy.

For the overall survival, there was no statistically significant difference between the study arms. The results on overall survival are fraught with uncertainty due to the different use of subsequent therapies between the study arms.

In terms of morbidity, the symptom scales of the EORTC QLQ-C30 pain and diarrhoea questionnaire show a minor disadvantage. In the other symptom scales of the EORTC QLQ-C30 and for the endpoint of health status (EQ-5D VAS), there was no relevant difference for the benefit assessment. An overall disadvantage is derived in the endpoint category of morbidity due to the disadvantage for pain and diarrhoea in the symptom scales of the EORTC QLQ-C30.

In terms of health-related quality of life, neither an advantage nor a disadvantage can be derived using the patient-reported endpoints (functional scales of the EORTC QLQ-C30, FACT-Lym).

With regard to the endpoint category of side effects, there were no statistically significant differences between the treatment arms for the overall rate of SAEs and severe AEs. For "Therapy discontinuation due to AEs", there was a disadvantage of the acalabrutinib combination. There were predominantly disadvantages of the acalabrutinib combination therapy for some of the specific AEs. A disadvantage is derived overall in the endpoint category of side effects due to the disadvantage in "Therapy discontinuation due to AEs".

In the overall analysis, there were no positive effects for patient-relevant endpoints. The endpoints "Pain" and "Diarrhoea" (EORTC QLQ-C30) showed adverse effects for acalabrutinib in combination with BR and a disadvantage in the side effects could also be found due to the increase in "Therapy discontinuation due to AEs". Taking into account the small extent of the adverse effects on symptoms, the uncertainties in overall survival and the limited reliability of data for the increase in therapy discontinuation due to AEs, the G-BA determined in a weighted decision that an additional benefit of acalabrutinib in combination with BR is not proven for the treatment of adults with untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant and for whom BR is an appropriate individualised therapy.

a2) Adults with untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant and for whom bendamustine in combination with rituximab is not an appropriate individualised therapy

An additional benefit is not proven.

Justification:

The ECHO study is unsuitable for deriving the additional benefit since only the combination of BR was used in the comparator arm of this study. An additional benefit is therefore not proven for adults for whom BR is not an appropriate individualised therapy.

2.1.4 Summary of the assessment

The present assessment is the assessment of the new therapeutic indication for the active ingredient acalabrutinib. Calquence in combination with bendamustine and rituximab (BR) is

indicated for the treatment of adults with previously untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant.

The G-BA determined the appropriate comparator therapy to be an individualised therapy with selection of several therapy options, including BR.

The results of the double-blind, randomised, controlled phase III ECHO study, in which acalabrutinib + BR was compared with BR, are available for the benefit assessment.

As only BR was offered as a comparator in the ECHO study, there was no selection of therapy options available that could have facilitated an individualised treatment decision. For this reason, the assessment is carried out separately for two patient groups in accordance with the suitability of BR as an individualised therapy.

a1) Adults with untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant and for whom bendamustine in combination with rituximab is an appropriate individualised therapy

a2) Adults with untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant and for whom bendamustine in combination with rituximab is not an appropriate individualised therapy

On patient group a1)

For the overall survival, there was no statistically significant difference between the study arms. The results on overall survival are fraught with uncertainty due to the different use of subsequent therapies between the study arms.

A disadvantage is derived overall for morbidity, based on the minor disadvantage in the symptom scales of the EORTC QLQ-C30 Pain and Diarrhoea and the absence of any relevant differences between the study arms in the other symptom scales of the EORTC QLQ-C30 and health status (EQ-5D VAS).

In terms of health-related quality of life, neither an advantage nor a disadvantage can be derived using the patient-reported endpoints (functional scales of the EORTC QLQ-C30, FACT-Lym).

With regard to the endpoint category of side effects, there were no statistically significant differences between the treatment arms for the overall rate of SAEs and severe AEs. For "Therapy discontinuation due to AEs", there was a disadvantage of the acalabrutinib combination. There were predominantly disadvantages of the acalabrutinib combination for some of the specific AEs. A disadvantage is derived overall in the endpoint category of side effects due to the disadvantage in "Therapy discontinuation due to AEs".

In the overall analysis, there were no positive effects for patient-relevant endpoints. The endpoints "Pain" and "Diarrhoea" (EORTC QLQ-C30) as well as "Therapy discontinuation due to AEs" show disadvantages of the acalabrutinib combination. Taking into account the small extent of the disadvantages for symptoms, the uncertainties in overall survival and the limited reliability of data for the increase in therapy discontinuation due to AEs, the G-BA determined in a weighted decision that an additional benefit of acalabrutinib in combination with BR is not proven for the treatment of adults with untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant and for whom BR is an appropriate individualised therapy.

On patient group a2)

In the ECHO study, treatment was offered exclusively with bendamustine in combination with rituximab (BR) as the comparator. Overall, no data are available for patients, for whom BR is not an appropriate individualised therapy, which is why an additional benefit for patient group a2) is not proven.

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

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

The resolution is based on the information from the addendum of IQWiG (addendum of 27 November 2025). In the written statement procedure, the pharmaceutical company submitted an updated calculation of patient numbers in the target population, which is derived from an incidence based on the German Centre for Cancer Registry Data (ZfKD) at the Robert Koch Institute (RKI). The submitted ZfKD data were only available to the pharmaceutical company after submission of the dossier. In the dossier, the first step was to determine patient numbers on the basis of data on non-Hodgkin lymphoma and to subsequently calculate the number of newly diagnosed patients in 2025 using gender-specific percentage values of mantle cell lymphoma.

A cumulative incidence for the years 2020-2023 (most recent data record) calculated on the basis of the subsequently submitted ZfKD data is used to differentiate how many subjects have started first-line therapy for mantle cell lymphoma.

In the overall analysis, the newly presented derivation is methodologically suitable in general for deriving the number of patients in the SHI target population. According to IQWiG's assessment (addendum of 27 November 2025), additional percentage values can be determined for patient groups a1) and a2), whereas the pharmaceutical company only presented them for the total population a). In the addendum of 27 November 2025, IQWiG calculates the patient numbers separately for patient groups a1) and a2) on the basis of these additional percentage values. The patient number in the SHI target population calculated in this way is used as the basis for this resolution. In total, this number is of comparable magnitude to that of the pharmaceutical company.

The patient number in the SHI target population is subject to uncertainty due to the following aspects:

- The incidence based on the ZfKD data from 2020 to 2023 is considered uncertain, as the criteria according to which the patients were selected in the data record were not presented in detail by the pharmaceutical company. In addition, the data record only contains data from the diagnosis year 2020 onwards, meaning that patients were not included who, for example, only started first-line therapy in 2023 after a longer watch-and-wait period following a diagnosis before 2020. In addition, it cannot be ruled out that all therapies and progression events were documented despite the reporting obligation.
- The newly presented lower limit for the percentage of subjects who are not eligible for autologous stem cell transplant tends to be underestimated on the basis of the ZfKD data presented and there is uncertainty as to which criteria were used to assess suitability for autologous stem cell transplant.
- The newly presented upper limit - excluding subjects with a poor general condition - for the percentage of subjects, who are not eligible for autologous stem cell transplant,

is considered uncertain, as the value does not relate exclusively to an age ≥ 65 years and may be higher if this age group alone is considered.

- In the breakdown of patient groups a1) and a2) according to suitability for bendamustine + rituximab (BR), there are uncertainties regarding the percentages based on a US cohort. These treatment data show the percentage of patients who received BR or another first-line therapy. The percentage of patients who have received first-line therapy with BR does not have to be the same as the percentage of those for whom BR is an appropriate individualised therapy. In addition, this cohort also included patients who were eligible for autologous stem cell transplant.

There are around 90 to 190 patients in patient group a1), for whom BR is an appropriate individualised therapy, and around 130 to 270 patients in patient group a2).

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: 30 September 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 mantle cell lymphoma.

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.

For the cost representation, one year is assumed for all medicinal products.

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

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.

Treatment period:

Adults with untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant

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	Continuously, 2 x daily	365	1	365
Bendamustine	1 x on day 1 and 2 of a 28-day cycle	6.0	2	12.0
Rituximab	1 x on day 1 of a 28-day cycle From cycle 8 (if applicable, maintenance): 1 x every 56 days	6.0 3.0	1	9.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Appropriate comparator therapy				
Individualised therapy with selection of				
Bendamustine + rituximab[5,6]				
Bendamustine	1 x on day 1 and 2 of a 28-day cycle	6.0	2	12.0
Rituximab	1 x on day 1 of a 28-day cycle From cycle 8 (if applicable, maintenance): 1 x every 56 days	6.0 3.0	1	6.0 - 9.0
R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)[7]				
Rituximab	Cycle 1–8: 1 x on day 0 of a 21-day cycle From cycle 9 (if applicable, maintenance): 1 x every 56 days	8.0 3.5	1	8.0 - 11.5
Cyclophosphamide	1 x on day 1 of a 21-day cycle	8.0	1	8.0
Doxorubicin	1 x on day 1 of a 21-day cycle	8.0	1	8.0
Vincristine	1 x on day 1 of a 21-day cycle	8.0	1	8.0

[5] Rummel et al.; Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet. 2013 Apr 6;381(9873):1203-10

[6] Rummel et al.; Two years Rituximab maintenance vs. observation after first line treatment with bendamustine plus rituximab (B-R) in patients with marginal zone lymphoma (MZL): results of a prospective, randomized, multicenter phase 2 study (the StiL NHL7-2008 MAINTAIN trial); Meeting Abstract: 2018 ASCO Annual Meeting I; https://ascopubs.org/doi/10.1200/JCO.2018.36.15_suppl.7515

[7] Annex VI to Section K of the Pharmaceuticals Directive (last revised: 29 August 2025)

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Prednisone	1 x on day 1-5 of a 21-day cycle	8.0	5	40.0
VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone)				
Bortezomib	4 x on day 1, 4, 8, 11 of a 21-day cycle	6.0 - 8.0	4	24.0 - 32.0
Rituximab	1 x on day 1 of a 21-day cycle	6.0 - 8.0	1	6.0 - 8.0
Cyclophosphamide	1 x on day 1 of a 21-day cycle	6.0 - 8.0	1	6.0 - 8.0
Doxorubicin	1 x on day 1 of a 21-day cycle	6.0 - 8.0	1	6.0 - 8.0
Prednisone	1 x on day 1-5 of a 21-day cycle	6.0 - 8.0	5	30.0 - 40.0

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).[8]

Adults with relapsed or refractory mantle cell lymphoma who have received at least one prior therapy with a Bruton's tyrosine kinase (BTK) inhibitor

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Acalabrutinib	100 mg	200 mg	2 x 100 mg	365	730 x 100 mg
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	375 mg/m² = 716.3 mg	716.3 mg	1 x 500 mg + 3 x 100 mg	6.0	6 x 500 mg + 18 x 100 mg
Maintenance with rituximab with complete or partial response					
Rituximab	375 mg/m² = 716.3 mg	716.3 mg	1 x 500 mg + 3 x 100 mg	3.0	3 x 500 mg + 9 x 100 mg
Appropriate comparator therapy					
Individualised therapy with selection of					
Bendamustine + rituximab[5,6]					
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	375 mg/m² = 716.3 mg	716.3 mg	1 x 500 mg + 3 x 100 mg	6.0 – 9.0	6 x 500 mg + 18 x 100 mg - 9.0 x 500 mg + 27 x 100 mg
R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)[7]					
Rituximab	375 mg/m² = 716.3 mg	716.3 mg	1 x 500 mg + 3 x 100 mg	8.0 - 11.5	8 x 500 mg + 24 x 100 mg - 11.5 x 500 mg + 34.5 x 100 mg

[8] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Cyclophosphamide	750 mg/m² = 1,432.5 mg	1,432.5 mg	1 x 2,000 mg	8.0	8.0 x 2,000 mg
Doxorubicin	50 mg/m² = 95.5 mg	95.5 mg	1 x 100 mg	8.0	8.0 x 100 mg
Vincristine	1.4 mg/m² = 2.7 mg (max. 2 mg)[7]	2.0 mg	1 x 2 mg	8.0	8.0 x 2 mg
Prednisone (PO)	100 mg	100 mg	2 x 50 mg	40.0	80.0 x 50 mg
VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone)					
Bortezomib	1.3 mg/m² = 2.5 mg	2.5 mg	1 x 2.5 mg	24.0 – 32.0	24.0 x 2.5 mg - 32.0 x 2.5 mg
Rituximab	375 mg/m² = 716.3 mg	716.3 mg	1 x 500 mg + 3 x 100 mg	6.0 - 8.0	6.0 x 500 mg + 18.0 x 100 mg - 8.0 x 500 mg 24.0 x 100 mg
Cyclophosphamide	750 mg/m² = 1,432.5 mg	1,432.5 mg	1 x 2,000 mg	6.0 - 8.0	6.0 x 2,000 mg - 8.0 x 2,000 mg
Doxorubicin	50 mg/m² = 95.5 mg	95.5 mg	1 x 100 mg	6.0 - 8.0	6.0 x 100 mg - 8.0 x 100 mg
Prednisone (PO)	100 mg/m² = 191.0 mg	191.0 mg	3 x 50 mg + 2 x 20 mg	30.0 - 40.0	90.0 x 50 mg + 60 x 20 mg - 120.0 x 50 mg + 80 x 20 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:

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
Bendamustine 100 mg	5 PIC	€ 1,653.78	€ 1.77	€ 208.35	€ 1,443.66
Bendamustine 100 mg	1 PIC	€ 337.73	€ 1.77	€ 41.31	€ 294.65
Bendamustine 25 mg	5 PIC	€ 422.90	€ 1.77	€ 52.08	€ 369.05
Bendamustine 25 mg	1 PIC	€ 101.23	€ 1.77	€ 11.38	€ 88.08
Rituximab 500 mg	1 CIS	€ 1,777.34	€ 1.77	€ 98.21	€ 1,677.36
Rituximab 100 mg	2 CIS	€ 717.21	€ 1.77	€ 39.08	€ 676.36
Appropriate comparator therapy					
Bendamustine 100 mg	5 PIC	€ 1,653.78	€ 1.77	€ 208.35	€ 1,443.66
Bendamustine 100 mg	1 PIC	€ 337.73	€ 1.77	€ 41.31	€ 294.65
Bendamustine 25 mg	5 PIC	€ 422.90	€ 1.77	€ 52.08	€ 369.05
Bendamustine 25 mg	1 PIC	€ 101.23	€ 1.77	€ 11.38	€ 88.08
Bortezomib 2,500 mg	1 PSI	€ 185.37	€ 1.77	€ 8.26	€ 175.34
Cyclophosphamide 2,000 mg	1 CII	€ 70.38	€ 1.77	€ 2.80	€ 65.81
Doxorubicin 100 mg[9]	1 CIS	€ 285.79	€ 1.77	€ 21.71	€ 262.31
Prednisone 50 mg[9]	50 TAB	€ 68.06	€ 1.77	€ 4.49	€ 61.80
Prednisone 50 mg[9]	10 TAB	€ 23.19	€ 1.77	€ 0.94	€ 20.48
Prednisone 20 mg[9]	100 TAB	€ 29.29	€ 1.77	€ 1.42	€ 26.10
Rituximab 500 mg	1 CIS	€ 1,777.34	€ 1.77	€ 98.21	€ 1,677.36
Rituximab 100 mg	2 CIS	€ 717.21	€ 1.77	€ 39.08	€ 676.36
Rituximab 500 mg[7]	1 CIS	€ 1,777.34	€ 1.77	€ 84.18	€ 1,691.39
Rituximab 100 mg[7]	2 CIS	€ 717.21	€ 1.77	€ 33.50	€ 681.94
Vincristine 2 mg	1 VIA	€ 39.04	€ 1.77	€ 2.23	€ 35.04
Abbreviations: VIA = vial; FCT = film-coated tablets; HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; SII = solution for injection/infusion; CII = concentrate for injection or infusion solution; PSI = powder for solution for injection; PIC = powder for the preparation of an infusion solution concentrate; TAB = tablets					

LAUER-TAXE® last revised: 15 October 2025

[9] Fixed reimbursement rate

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.

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.

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 with an analgesic/ antipyretic and an antihistamine should always be administered prior to each application of rituximab. The costs of this premedication cannot be quantified as there is no dosage information that allows cost representation.

Screening for hepatitis B virus (HBV)

Patients should be tested for hepatitis B infection prior to 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 constellations, further steps may be necessary in accordance with current guideline recommendations.[10]

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.

[10] 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 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:

a) Adults with untreated mantle cell lymphoma who are not eligible for autologous stem cell transplant

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

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

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 August 2024, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 27 May 2025.

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 5b VerfO.

By letter dated 30 June 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 25 September 2025, and the written statement procedure was initiated with publication on the G-BA website on 1 October 2025. The deadline for submitting written 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 of data submitted in the written statement procedure. The addendum prepared by the IQWiG was submitted to the G-BA on 27 November 2025 and 28 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 August 2024	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	27 May 2025	New 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	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