Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Acalabrutinib (chronic lymphocytic leukaemia (CLL), as monotherapy, first-line)

of 3 June 2021

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1. Legal basis

According to Section 35a (1) SGB V, the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first submission 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 of the medical product 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 statutory health insurance funds,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the market of the combination of active ingredient acalabrutinib in accordance with Chapter 5, Section 8, paragraph 1, number 1, of the Rules of Procedure of the G-BA (VerfO) is 1 December 2020. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 30 November 2020.

The G-BA commissioned IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 March 2021 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. An oral hearing was also 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 has assesses 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 has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of acalabrutinib (Calquence) in accordance with the product information

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

Calquence as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior treatment.

Therapeutic indication of the resolution (resolution of 3/6/2021):

Calquence as monotherapy is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with previously untreated chronic lymphocytic leukaemia who do not have a 17p deletion or TP53-mutation and who are eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

Appropriate comparator therapy:

- Fludarabine in combination with cyclophosphamide and rituximab (FCR)

b) Adult patients with previously untreated chronic lymphocytic leukaemia who do not have a 17p deletion or TP53-mutation and who are not eligible for therapy with FCR

Appropriate comparator therapy:

- Bendamustine in combination with rituximab

or

1 General Methods, version 6.0 from 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

- Chlorambucil in combination with rituximab or obinutuzumab

c) Adult patients with previously untreated chronic lymphocytic leukaemia with 17p deletion and/or TP53-mutation or unsuitable for chemoimmunotherapy due to other reasons

Appropriate comparator therapy:

- Ibrutinib

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

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

In determining the appropriate comparator therapy, the following criteria, in particular, must be considered 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 Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. Approved for this therapeutic indication are acalabrutinib, ibrutinib, idelalisib and venetoclax; the anti-CD-20 antibodies obinutuzumab and rituximab; the cytostatics bendamustine, chlorambucil, cyclophosphamide and fludarabine; as well as the glucocorticoids prednisone and prednisolone. The chronic lymphocytic leukaemia is assigned to the non-Hodgkin lymphoma. Accordingly, the substances doxorubicin, etoposide, mitoxantrone, vinblastine and vincristine are also approved. The approvals are partly tied to certain combination partners.

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

- Ibrutinib (resolutions dated 1 April 2021, 20 February 2020, 15 December 2016 and 21 July 2016)
- Idelalisib (resolution of 16 March 2017)
- Obinutuzumab (resolution of 5 February 2015)
- Venetoclax (resolutions of 15 October 2020 and 16 May 2019)

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication.

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

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

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 health care provision.

According to the available evidence, patients with previously untreated chronic lymphocytic leukaemia without 17p deletion or TP53-mutation who are physically fit are primarily treated with intensive chemoimmunotherapy consisting of fludarabine, cyclophosphamide and rituximab (FCR). To assess whether a patient can be treated with FCR, the general condition, co-morbidities, organ functions and age are all taken into consideration.

For ibrutinib in combination with rituximab, a hint of considerable additional benefit was identified by resolution of 1 April 2021 for the subpopulation of patients eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR). Ibrutinib in combination with rituximab is a new treatment option whose therapeutic value cannot yet be conclusively assessed.

If patients cannot be treated with FCR chemoimmunotherapy (subpopulation b), guidelines recommend a combination therapy consisting of a BTK inhibitor, venetoclax or a chemotherapeutic agent and a CD20 antibody. According to the marketing authorisation, ibrutinib in combination with rituximab or in combination with obinutuzumab, venetoclax in combination with obinutuzumab or bendamustine in combination with rituximab as well as chlorambucil in combination with either rituximab or obinutuzumab can be considered. According to the statements of the AkdÄ, a monotherapy with ibrutinib or a combination therapy consisting of ibrutinib or venetoclax and a monoclonal antibody against CD20 can also be considered for patients in good general condition. Regarding the use of ibrutinib, however, the AkdÄ points out that the guidelines on which it is based have not yet taken into consideration in more recent results on sometimes severe cardiovascular side effects. For ibrutinib monotherapy, no additional benefit could be determined in the benefit assessment published in the decision of 15 December 2016 in the respective subpopulations. In the resolution of 20 February 2020, hint of a minor additional benefit was determined for ibrutinib in combination with the anti-CD20 moAK obinutuzumab in the sub-population of patients who are not eligible for therapy with FCR. This additional benefit was based

on an advantage in the side effects category, although conclusions could only be made for the first 6 months of therapy on the basis of the time-to-event analysis presented. For the combination of ibrutinib and rituximab, the resolution of 1 April 2021 did not provide evidence of additional benefit for the subpopulation of patients who are not eligible for therapy with FCR due to a lack of data. The combination of venetoclax and the anti-CD20-MoAb obinutuzumab is a relatively new therapeutic option. By resolution of 15 October 2020, no additional benefit was also identified for the respective subpopulations. Overall, the G-BA does not currently consider ibrutinib as monotherapy or in combination with obinutuzumab or rituximab and venetoclax in combination with obinutuzumab to be an appropriate comparator therapy, both in the subpopulation of patients eligible for therapy with FCR and in the subpopulation of patients not eligible for therapy with FCR. In accordance with the recommendations from guidelines and taking into account the respective authorisation status, the combinations bendamustine in combination with rituximab, chlorambucil in combination with rituximab, chlorambucil in combination with rituximab or chlorambucil in combination with obinutuzumab are equally appropriate treatment options for patients who are not eligible for therapy with FCR.

On the other hand, for patients with a 17p deletion and/or a TP53-mutation, these guidelines provide a clear recommendation for therapy with ibrutinib in accordance with the statements of the AkdÄ. The reason is that these patients under treatment with chemoimmunotherapy generally have a poor response rate, a comparatively rapid occurrence of relapses and a comparatively low life expectancy. In addition to ibrutinib and venetoclax monotherapy, further ingredients are approved for this patient group: idelalisib in combination with rituximab, venetoclax in combination with obinutuzumab and ibrutinib in combination with obinutuzumab or rituximab, other active ingredients for this patient group. However, the guideline recommendations as well as the statements of the AkdÄ primarily focus on ibrutinib. Taking into consideration the recommendations and the benefit assessments conducted, as well as the approved therapeutic indications of the active ingredients and combinations of active ingredients, ibrutinib alone is determined as the appropriate comparator therapy for this patient population.

Therapy options are limited for patients without a 17p deletion or TP53 mutation for whom chemoimmunotherapy is unsuitable, e.g. because of their poor general condition or contraindications. Based of the existing evidence, the G-BA considers it appropriate to also designate ibrutinib as an appropriate comparator therapy for this patient group.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment order.

2.1.3 Extent and probability of the additional benefit

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

a) <u>Adult patients with previously untreated chronic lymphocytic leukaemia who do not have a 17p deletion or TP53-mutation and who are eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)</u>

For acalabrutinib for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia who do not have a 17p deletion or TP53-mutation and for whom therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR) is an option, an additional benefit is not proven.

Justification:

The pharmaceutical company did not present any data that would have been suitable for the assessment of the additional benefit compared with the appropriate comparator therapy.

b) Adult patients with previously untreated chronic lymphocytic leukaemia who do not have a 17p deletion or TP53-mutation and for whom therapy with FCR is not an option

For acalabrutinib for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia who do not have a 17p deletion or TP53 mutation and for whom therapy with FCR is not an option, there is a hint of a minor additional benefit.

Justification:

The benefit assessment is based on the results of the ongoing, open-label, randomised ACE-CL-007 (ELEVATE-TN) study, which compares acalabrutinib or acalabrutinib in combination with obinutuzumab with chlorambucil in combination with obinutuzumab (chlorambucil + obinutuzumab). The treatment arms acalabrutinib and chlorambucil + obinutuzumab are relevant for the present benefit assessment.

Adult patients with previously untreated and treatment-naive cluster-of-differentiation (CD)20+ CLL according to International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) criteria (2008) were included. Patients were required to have an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0-2 onwards and were also required to be ≥ 65 years of age. Younger patients had to have renal dysfunction (creatinine clearance of 30-69 ml/min estimated by Cockroft-Gault equation) and/or co-morbidities defined by a Cumulative Illness Rating Scale for Geriatrics (CIRS G) of > 6.

A total of 179 patients were randomised to the acalabrutinib intervention arm and 177 to the chlorambucil + obinutuzumab comparator arm. Stratification factors were presence of 17p deletion (yes vs no), ECOG-PS (0-1 vs 2), and geographic region (North America, Western Europe vs other).

Patients were included regardless of whether they were eligible for FCR therapy or not. To create an appropriate subpopulation of patients for whom FCR therapy is not an option, the pharmaceutical company uses renal function (creatinine clearance < 70 ml/min) as a sufficient criterion and the following combined criteria (if ≥ 2 criteria are met, FCR therapy is no longer an option): Age (> 65), general condition (ECOG-PS ≥ 2), anaemia and/or thrombocytopenia, co-morbidities (CIRS-G > 6). The pharmaceutical company excludes patients with a 17p deletion and/or TP53-mutation for this subpopulation. Therefore, the pharmaceutical company followed the procedure in previous benefit assessments. This results in 103 patients in the acalabrutinib arm and 95 patients in the chlorambucil + obinutuzumab arm for the relevant subpopulation. The mean age of the predominantly male study participants was 72 years in the intervention arm and 73 years in the comparison arm.

In the intervention arm, treatment with acalabrutinib was continued until disease progression or unacceptable toxicity. In the comparator arm, chlorambucil and obinutuzumab were each

administered for a maximum of 6 cycles (28 days each) in the absence of disease progression or unacceptable toxicities. After disease progression, patients in the comparator arm were eligible to receive acalabrutinib as monotherapy.

The pharmaceutical company does not provide information on the treatment duration for the relevant subpopulation in the dossier. During the written statement procedure, the pharmaceutical company submitted data on the treatment duration for the relevant subpopulation. As of the 1/8/2019 data cut-off, treatment in the intervention arm of the relevant subpopulation was approximately 6 times longer than in the comparator arm.

The pharmaceutical company submitted results for 2 data cut-offs. For the endpoints of the endpoint category Mortality, Morbidity, and Health-related quality of life, analysis are available for the first year of the study. Data cut-off from 8.2.2019 available, for the endpoint category Side effects for the 2nd Data cut-off as of 1/8/2019: These data cut-offs are used for the present benefit assessment.

Extent and probability of the additional benefit

Mortality

Overall survival

In the ELEVATE-TN study, the endpoint Overall survival is defined as time from randomisation to death from any cause.

There are no signs of statistically significant differences between the treatment groups.

Morbidity

Progression-free survival

Progression-free survival (PFS) is the primary endpoint in the ELEVATE-TN study and was assessed by an independent review committee (IRC) according to iwCLL criteria. The PFS is operationalised as the time from randomisation to disease progression or death from any cause.

The acalabrutinib arm showed significantly longer progression-free survival than the comparator arm chlorambucil + obinutuzumab.

The PFS endpoint is a combined endpoint composed of endpoints of the “Mortality” and “Morbidity” categories. The “Mortality” endpoint component is already assessed via the “overall survival” endpoint as an independent endpoint. The morbidity component “Disease progression” is assessed according to IWCL criteria and thus predominantly by means of laboratory parametric, imaging and haematological procedures. Taking into consideration the aforementioned aspects, there are different views within the G-BA regarding the patient relevance of the endpoint PFS. The overall statement on the additional benefit remains unaffected.

Fatigue (FACIT-Fatigue)

In the ELEVATE-TN study, FACIT fatigue was assessed until disease progression.

In the dossier, the pharmaceutical company submitted both responder analysis operationalised as time to clinically relevant improvement or worsening by ≥ 3 points. Furthermore, the pharmaceutical company submitted evaluations of the mean amendment based on a mixed-effect model with repeated measurements (MMRM).

For the evaluations of the responder analysis, the pharmaceutical company only considered time points with a return rate ≥ 70% in both treatment groups, so that available data of a period of about one year were not considered.

For the evaluations on mean changes, the pharmaceutical company only considers time points with a return rate ≥ 70% in both treatment groups and a change from baseline for at least 10% of the patients in both treatment groups.

During the written statement procedure, the pharmaceutical company submits MMRM evaluations without the minimum requirement of 10% change from baseline as well as responder analysis with 15% of the scale span covering all survey time points regardless of return rates. Responder analysis are operationalised as time to 1. deterioration by ≥ 15% of scale range compared to baseline (Global Fatigue Score: ≥ 7.8 points [scale range: 0-52]. There are no statistically significant differences between the treatment groups.

The evaluations of the subscales Fatigue Symptomatology Score and Fatigue Impact Score presented in the written statement procedure are not used due to a lack of information on the evaluation of subscales of the FACIT-Fatigue.

Disease-related symptomatology

In the ELEVATE-TN study, disease-related symptomatology (fatigue, fever, night sweats, weight loss) were recorded during the course of the study.

In the dossier, the pharmaceutical company did not submit any evaluations.

Within the framework of the written statement procedure, the pharmaceutical company submitted evaluations on the endpoint “Disease-related symptoms”. These included the following symptoms in the ELEVATE-TN study: unintentional weight loss of ≥ 10% within the past 6 months, significant fatigue (e.g., Eastern Cooperative Oncology Group Performance Status [ECOG-PS] ≥ 2, inability to work or perform usual activities), fever > 38 °C for more than 2 weeks without evidence of infection and night sweats for more than 1 month without evidence of infection.

The pharmaceutical company submits evaluations operationalised as time to 1st dose. Absence of any disease-related symptoms in patients who had at least 1 disease-related symptomatology at baseline. Therefore, a statement for all patients of the relevant sub-population is not possible, and the presented evaluations are not used.

Symptomatology (EORTC QLQ-C30)

In the ELEVATE-TN study, symptoms were assessed using the EORTC QLQ-C30 symptom scales until disease progression.

In the dossier, the pharmaceutical company submitted both responder analysis operationalised as time to clinically relevant improvement or worsening by ≥ 10 points. Furthermore, the pharmaceutical company submitted evaluations of the mean amendment based on a mixed-effect model with repeated measurements (MMRM).

For the evaluations of the responder analysis, the pharmaceutical company considered time points with a return rate ≥ 70% in both treatment groups, so that available data of a period of about one year were not considered.

For the mean change evaluations, the pharmaceutical company considers time points with a return rate ≥ 70% in both treatment groups and a change from baseline for at least 10% of patients in both treatment groups.

During the written statement procedure, the pharmaceutical company submits MMRM evaluations without the minimum requirement of 10% change from baseline as well as responder analysis with 15% of the scale span covering all survey time points regardless of return rates. Responder analysis are operationalised as time to 1. deterioration by ≥ 15 points compared with baseline (scale range: 0-100). There are no statistically significant differences between the treatment groups.

Health status (EQ-5D VAS)

Health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire until disease progression.

In the dossier, the pharmaceutical company submitted both responder analysis, operationalised as time to improvement or worsening by ≥ 7 points and by ≥ 10 points, respectively. Furthermore, the pharmaceutical company submitted evaluations of the mean amendment based on a mixed-effect model with repeated measurements (MMRM).

For the evaluations of the responder analysis, the pharmaceutical company considered time points with a return rate ≥ 70% in both treatment groups, so that available data of a period of about one year were not considered.

For the mean change evaluations, the pharmaceutical company considers time points with a return rate ≥ 70% in both treatment groups and a change from baseline for at least 10% of patients in both treatment groups.

During the written statement procedure, the pharmaceutical company submits MMRM evaluations without the minimum requirement of 10% change from baseline as well as responder analysis with 15% of the scale span covering all survey time points regardless of return rates. Responder analysis are operationalised as time to 1. deterioration by ≥ 15 points compared with baseline (scale range: 0-100). There is a statistically significant difference to the benefit of acalabrutinib.

Quality of life

EORTC QLQ-C30 (functional scales)

Health-related quality of life will be assessed in the ELEVATE-TN study using the EORTC QLQ-C30 functional scales until disease progression.

In the dossier, the pharmaceutical company submitted both responder analysis operationalised as time to clinically relevant improvement or worsening by ≥ 10 points. Furthermore, the pharmaceutical company submitted evaluations of the mean amendment based on a mixed-effect model with repeated measurements (MMRM).

For the evaluations of the responder analysis, the pharmaceutical company considered time points with a return rate ≥ 70% in both treatment groups, so that available data of a period of about one year were not considered.

For the mean change evaluations, the pharmaceutical company considers time points with a return rate ≥ 70% in both treatment groups and a change from baseline for at least 10% of patients in both treatment groups.

During the written statement procedure, the pharmaceutical company submits MMRM evaluations without the minimum requirement of 10% change from baseline as well as responder analysis with 15% of the scale span covering all survey time points regardless of return rates. Responder analysis are operationalised as time to 1. deterioration by ≥ 15 points

compared with baseline (scale range: 0-100). There are no statistically significant differences between the treatment groups.

Side effects

Side effects were assessed in both treatment groups up to 30 days after the last dose of study medication. Due to the different duration of observation in the treatment groups, the median duration of observation for this endpoint diverged significantly in both treatment groups (33.4 months in the intervention arm vs 6.1 months in the control arm). Therefore, the hazard ratio (HR) represents only about the first 7 months.

Adverse events (AE) in total

Nearly all study participants experienced an adverse event. These are only presented in a supplementary manner.

Serious adverse events (SAEs)

For the endpoint Hospitalisation no statistically significant difference was detected between the treatment groups.

Severe AE (CTCAE grade ≥ 3)

For the endpoint Severe AEs (CTCAE grade ≥ 3), there is a statistically significant difference in the benefit of acalabrutinib compared to chlorambucil + obinutuzumab.

Discontinuation due to AEs (≥ 1 component)

For the endpoint discontinuation due to AEs (≥ 1 component), there is a statistically significant difference in the benefit of acalabrutinib compared to chlorambucil + obinutuzumab.

Specific AEs

In detail, the specific adverse events for the endpoints "Nausea" (PT, AE), "Blood and lymphatic system disorders" (SOC, serious AEs), including "febrile neutropenia" (PT, serious AEs), and "metabolism and nutrition disorders" (SOC, serious AEs), including "tumour lysis syndrome" (PT, serious AEs), in each case a statistically significant difference to the benefit of acalabrutinib compared to chlorambucil + obinutuzumab.

For the endpoints "infections and infestations" (SOC, AEs) and "cardiac disorders" (SOC, AEs), there was no statistically significant difference between the treatment groups.

As no event occurred in the comparator arm, no time-to-event analysis can be performed for the endpoint "Bleeding" (SMQ, severe AEs)".

In the overall view of the endpoints on side effects, there were exclusively advantages for acalabrutinib compared to chlorambucil + obinutuzumab. These are evident in severe AEs (CTCAE CTCAE grade ≥ 3), discontinuation due to AEs, and in detail specific AEs. Due to the short observation period in the comparator arm, comparator statements based on the time-to-event analysis can only be derived for the period of the first 7 months of therapy. Comparator statements on long-term side effects cannot be made on the basis of the data.

Overall assessment

For the evaluation of the additional benefit of acalabrutinib for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) who do not have a 17p deletion or TP53-mutation and for whom therapy with FCR is not an option, data from a relevant subpopulation (patients who are not eligible for therapy with FCR) from the ELEVATE-TN study are available on mortality, morbidity, health-related quality of life and side effects compared with chlorambucil in combination with obinutuzumab.

For the endpoint overall survival, there is no statistically significant difference between the two treatment groups. An additional benefit in terms of overall survival is therefore not proven.

For the endpoints of the morbidity category, measured by the FACIT-Fatigue, EORTC-QLQ-C30 and the EQ-5D visual analogue scale, only the EQ-5D VAS showed a significant difference to the benefit of acalabrutinib.

There was no significant difference between treatment groups in health-related quality of life data collected using the EORTC-QLQ-C30.

In the Side effects category, benefits with acalabrutinib are seen in severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs. These are particularly evident in relation to acute side effects. In detail, the examination of the specific AEs also shows advantages exclusively in the intervention arm. However, due to the short observation period in the comparator arm, comparator statements based on the time-to-event analysis can only be derived for the period of the first 7 months of therapy.

Overall, there is therefore a clear advantage in Morbidity and in the category Side effects.

Overall, on the basis of the available data, a minor additional benefit can be derived for acalabrutinib compared to chlorambucil + obinutuzumab for adult patients with previously untreated chronic lymphocytic leukaemia who do not have a 17p deletion or TP53 mutation and for whom therapy with FCR is not an option.

Reliability of data (probability of additional benefit)

The present evaluation is based on the results of the ELEVATE-TN open-label randomised trial.

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

Due to the open study design, all endpoints have a high risk of bias, except for the endpoints overall survival and the endpoints on severe UEs (CTCAE grade ≥ 3).

In addition, the results for the endpoints in the side effects category, which are the main reasons for the additional benefit, are uncertain due to the short observation period in the control arm. As a result, only comparative statements for the period of the first 7 months after randomisation can be derived on the basis of the time-to-event analyses.

Therefore, the reliability of data for the additional benefit determined is classified in the category “hint”.

c) Adult patients with previously untreated chronic lymphocytic leukaemia with 17p deletion and/or TP53-mutation or unsuitable for chemoimmunotherapy due to other reasons

For acalabrutinib for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia with 17p deletion or TP53-mutation or for whom chemoimmunotherapy is not indicated for other reasons, an additional benefit is not proven.

Justification:

The pharmaceutical company did not present any data that would have been suitable for the assessment of the additional benefit compared with the appropriate comparator therapy.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient acalabrutinib: Calquence as monotherapy is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL).

In the therapeutic indication to be considered, three patient groups were distinguished:

a) Adult patients with previously untreated chronic lymphocytic leukaemia who do not have a 17p deletion or TP53-mutation and who are eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)

b) Adult patients with previously untreated chronic lymphocytic leukaemia who do not have a 17p deletion or TP53-mutation and for whom therapy with FCR is not an option

c) Adult patients with previously untreated chronic lymphocytic leukaemia with 17p deletion and/or TP53-mutation or unsuitable for chemoimmunotherapy due to other reasons.

Patient group a)

The appropriate comparator therapy was determined as follows by the G-BA:

- Fludarabine in combination with cyclophosphamide and rituximab (FCR)

The pharmaceutical company did not submit any data to prove the additional benefit. Thus, an additional benefit is not proven.

Patient group b)

The appropriate comparator therapy was determined as follows by the G-BA:

- bendamustine in combination with rituximab

or

- chlorambucil in combination with rituximab or obinutuzumab

The pharmaceutical company submits data from a relevant subpopulation (patients not eligible for therapy with FCR) of the ELEVATE-TN study (acalabrutinib vs chlorambucil + obinutuzumab).

There is no statistically significant difference in overall survival between the two treatment groups.

In the morbidity endpoint category, there is a benefit for acalabrutinib for the EQ-5D VAS endpoint.

In the endpoint category Side effects there are advantages with regard to severe AEs and discontinuation due to AEs. These are particularly evident in relation to acute side effects. In detail, the specific AEs also show advantages exclusively for acalabrutinib.

For the endpoints in the category Side effects, uncertainties arise due to the short observation time in the control arm. As a result, only comparative statements for the period of the first 7 months after randomisation can be derived on the basis of the time-to-event analyses.

Overall, a hint of a minor additional benefit for acalabrutinib is identified.

Patient group c)

The appropriate comparator therapy was determined as follows by the G-BA:

- Ibrutinib

The pharmaceutical company did not submit any data to prove the additional benefit. Thus, an additional benefit 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 patient numbers stated in the pharmaceutical company's dossier are based on data available in the benefit assessment of ibrutinib in combination with obinutuzumab (resolution of 20 February 2020) or obinutuzumab (resolution of 5 February 2015). In addition, the pharmaceutical company consulted a database analysis (Oncology Dynamics study, IQVIA).

As already stated in relation to the resolution of 15 December 2016, the derivation is subject to uncertainties. An overestimation tends to be assumed for patient group 1. This tends to result in an underestimation for patient groups 2 and 3. The patient numbers based on the database analysis show uncertainties regarding the allocation to the patient groups.

Based on the available data in the dossier, there is uncertainty as to whether, for each patient group, the proportion value-based either on the dossier on ibrutinib (resolution of 20 February 2020) or on the database analysis is a better approximation of the respective true value.

Within the framework of the written statement procedure, the pharmaceutical company submits patient figures, which are given as ranges.

For patient groups 1 and 3, the ranges of patient numbers estimated by the pharmaceutical company are more appropriate estimates.

For patient group 2, both the lower and upper bounds represent underestimates, so the upper bound is preferred as the minimum number.

Uncertainties remain, particularly with regard to the age of the data sources in the case of dynamic therapy development in the present therapeutic indication.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be considered. 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: 11 March 2021):
https://www.ema.europa.eu/documents/product-information/calquence-epar-product-information_de.pdf

Initiation and monitoring of treatment with acalabrutinib should be performed only by specialists in internal medicine and haematology and oncology experienced in the therapy 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 May 2021).

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 patient-

individual 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.

Treatment duration:

Name of therapy	Treatment mode	Number of treatments/patient/ year	Treatment duration/treatment (days)	Days of treatment/patient/ Year
Medicinal product to be assessed				
Acalabrutinib	continuously, twice daily	365	1	365
Appropriate comparator therapy				
a) Adult patients with previously untreated chronic lymphocytic leukaemia who do not have a 17p deletion or TP53-mutation and who are eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)				
Fludarabin + cyclophosphamide + rituximab (FCR)[2]				
Fludarabine	Day 1, 2 and 3 of 28 day cycle	6 cycles	3	18
Cyclophosphamide	Day 1, 2 and 3 of 28 day cycle	6 cycles	3	18
Rituximab	Day 1 of 28 day cycle	6 cycles	1	6
b) Adult patients with previously untreated chronic lymphocytic leukaemia who do not have a 17p deletion or TP53-mutation and for whom therapy with FCR is not an option				
Bendamustine + rituximab (BR)[3]				
Bendamustine	Day 1 and 2 of 28 day cycle	6 cycles	2	12
Rituximab	Day 1 of 28 day cycle	6 cycles	1	6
Chlorambucil + rituximab (CIR)[4]				

2 The basis for the calculation is the total consumption for a complete treatment over 6 cycles.
3 Fischer K et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukaemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukaemia Study Group. J Clin Oncol. 10 Sep 2011; 29(26):3559-66

Name of therapy	Treatment mode	Number of treatments/patient/ year	Treatment duration/treatment (days)	Days of treatment/patient/ Year
Chlorambucil	Day 1 and 15 of 28 day cycle	6 cycles	2	12
Rituximab	Day 1 of 28 day cycle	6 cycles	1	6
Chlorambucil + obinutuzumab[4]				
Chlorambucil	Day 1 and 15 of 28 day cycle	6 cycles	2	12
Obinutuzumab	Cycle 1: Day 1+ 2, 8 and 15, cycle 2 – 6: Day 1 of 28 day cycle each	6 cycles	4 (cycle 1) 1 (cycle 2– 6)	9
c) Adult patients with previously untreated chronic lymphocytic leukaemia with 17p deletion and/or TP53-mutation or unsuitable for chemoimmunotherapy due to other reasons.				
Ibrutinib				
Ibrutinib	continuously, Once daily	365	1	365

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were used as a basis (average height: 1.72 m, average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916).

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

Name of therapy	Dosage/ Application	Dosage/patient/days of treatment	Usage by strength/day of treatment	Days of treatment/ 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
Appropriate comparator therapy					
a) Adult patients with previously untreated chronic lymphocytic leukaemia who do not have a 17p deletion or TP53-mutation and who are eligible for therapy with fludarabine in combination with cyclophosphamide and rituximab (FCR)					
Fludarabin + cyclophosphamide + rituximab (FCR)					
Fludarabine	25 mg/m^2	47.5 mg	1 x 50 mg	18	18 x 50 mg
Cyclo-phosphamide	250 mg/m^2	475 mg	1 x 500 mg	18	18 x 500 mg
Rituximab	Cycle 1: 375 mg/m^2 Cycle 2–6: 500 mg/m^2	Cycle 1: 712.5 mg Cycle 2-6: 950 mg	Cycle 1: 3 x 100 mg 1 x 500 mg Cycle 2–6: 2 x 500 mg	6	3 x 100 mg 11 x 500 mg
b) Adult patients with previously untreated chronic lymphocytic leukaemia who do not have a 17p deletion or TP53-mutation and for whom therapy with FCR is not an option					
Bendamustine + rituximab (BR)					
Bendamustine	70 mg/m^2	133 mg	6 x 25 mg	12	72 x 25mg
Rituximab	Cycle 1: 375 mg/m^2 Cycle 2–6: 500 mg/m^2	Cycle 1: 712.5 mg Cycle 2-6: 950 mg	Cycle 1: 3 x 100 mg 1 x 500 mg Cycle 2–6: 2 x 500 mg	6	3 x 100 mg 11 x 500 mg
Chlorambucil + rituximab (ClbR)					
Chlorambucil	0.5 mg/kg	38.5 mg	19 x 2 mg	12	228 x 2 mg
Rituximab	Cycle 1: 375 mg/m^2 Cycle 2–6: 500 mg/m^2	Cycle 1: 712.5 mg Cycle 2-6: 950 mg	Cycle 1: 3 x 100 mg 1 x 500 mg Cycle 2–6: 2 x 500 mg	6	3 x 100 mg 11 x 500 mg
Chlorambucil + obinutuzumab					

Name of therapy	Dosage/ Application	Dosage/patient/days of treatment	Usage by strength/day of treatment	Days of treatment/ Patient/ Year	Average annual consumption by potency
Chlorambucil	0.5 mg/kg	38.5 mg	19 x 2 mg	12	228 x 2 mg
Obinutu-zumab	Cycle 1: Day 1: 100 mg Day 2: 900 mg Day 8: 1,000 mg Day 15: 1,000 mg Cycle 2–6 Day 1: 1,000 mg	1,000 mg	1 x 1,000 mg	9	8 x 1,000 mg
c) Adult patients with previously untreated chronic lymphocytic leukaemia with 17p deletion and/or TP53-mutation or unsuitable for chemoimmunotherapy due to other reasons.					
Ibrutinib					
Ibrutinib	420 mg	420 mg	1 x 420 mg	365	365 x 420 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 Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular strength was first determined on the basis of consumption. Having determined the number of packs of a particular strength, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Cost of medicinal product:

Name of therapy	Package size	Cost (pharmacy discount price)	Rebate § 130 SGB V	Rebate Section 130a SGB V	Cost after deduction of statutory rebates
Medicinal product to be assessed					
Acalabrutinib	60 HKP	€ 8,791.76	€ 1.77	€ 498.82	€ 8,291.17
Appropriate comparator therapy					

Name of therapy	Package size	Cost (pharmacy discount price)	Rebate § 130 SGB V	Rebate Section 130a SGB V	Cost after deduction of statutory rebates
Bendamustine 25 mg	5 PIK	€ 402.03	€ 1.77	€ 49.49	€ 350.77
Chlorambucil 2 mg	50 FCT	€ 36.31	€ 1.77	€ 1.40	€ 33.14
Cyclophosphamide 500 mg	6 PIJ	€ 81.98	€ 1.77	€ 8.98	€ 71.23
Fludarabine 50 mg	5 DSS	€ 546.58	€ 1.77	€ 25.41	€ 519.40
Fludarabine 50 mg	1 KII	€ 118.26	€ 1.77	€ 5.09	€ 111.40
Ibrutinib 420 mg	28 FCT	€ 5,772.62	€ 1.77	€ 0.00	€ 5,770.85
Obinutuzumab 1000 mg	1 IFK	€ 3,489.34	€ 1.77	€ 0.00	€ 3,487.57
Rituximab 100 mg	2 IFK	€ 716.94	€ 1.77	€ 39.08	€ 676.09
Rituximab 500 mg	1 IFK	€ 1,777.06	€ 1.77	€ 98.21	€ 1,677.08
Abbreviations: FTA = film-coated tablets; HC = Hard capsules; IFC = concentrate for the preparation of an infusion solution; PIE = powder for concentrate for solution for infusion, PIC = powder for the preparation of an infusion solution concentrate; DSS = dry substance without solvent					

LAUER-TAXE® last revised: 15 May 2021

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 considered as costs for additionally required SHI services.

Medical treatment costs, medical fees and costs incurred for routine examinations (e.g. regular laboratory services such as blood count examinations) that do not exceed the scope of normal expenses in the course of treatment are not shown.

Designation of the therapy	Type of service	Costs per pack or service	Days of treatment/year	Annual costs/patient
Medicinal product to be assessed				
Acalabrutinib	*HBV test* Hepatitis B surface antigen status (GOP number 32781)	€ 5.50	1	€ 5.50
	Hepatitis B antibody status (GOP number 32614)	€ 5.90	1	€ 5.90
Appropriate comparator therapy				
Ibrutinib	*HBV test* Hepatitis B surface antigen status (GOP number 32781)	€ 5.50	1	€ 5.50
	Hepatitis B antibody status (GOP number 32614)	€ 5.90	1	€ 5.90
Rituximab	*HBV test*	€ 5.50	1	€ 5.50

	Hepatitis B surface antigen status (GOP number 32781)			
	Hepatitis B antibody status (GOP number 32614)	€ 5.90	1	€ 5.90
	Premedication Antihistamines e.g. Dimetinden i.v. 4 mg Antipyretics e.g. paracetamol 2 x 500 mg	 € 14.93 € 1.36[5,6]	 6 6	 € 44.79 € 1.36
Obinutuzumab	*HBV test* Hepatitis B surface antigen status (GOP number 32781)	€ 5.50	1	€ 5.50
	Hepatitis B antibody status (GOP number 32614)	€ 5.90	1	€ 5.90
	Premedication Corticosteroid e.g. dexamethasone 5 x 4 mg Antihistamines e.g. Dimetinden i.v. 4 mg Antipyretics e.g. paracetamol 2 x 500 mg	 € 14.44[5] € 14.93 € 1.36[5.6]	 9 9 9	 € 72.20 € 59.72 € 1.36

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 1.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatics amount to a maximum of € 81 per ready-to-use preparation, and for the production of parenteral solutions with monoclonal antibodies to a maximum of € 71 per ready-to-use unit. These additional miscellaneous costs do not add to the pharmacy sales price, but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (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 sales price of the active ingredient, the invoicing of discards, the calculation of

On the basis of a fixed amount

6 Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Section 12, paragraph 7, of the AM-RL (information as accompanying medication in the product information of the prescription medicinal product) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5a SGB V, when a non-prescription medicinal product is dispensed invoiced according Section 300, a medicinal product sale price applies to the insured person in the amount of the sale price of the pharmaceutical company plus the surcharges according to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the valid version of 31 December 2003: FB Paracetamol tablets 20 pieces = 1.50 € (pharmacy discount according to Section 130 paragraph 1 and 2, 5% from FB; manufacturer discount = 0.06 €)

application containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs retail pharmacist services (Hilfstaxe).

3. Bureaucratic cost calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 22 December 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 30 November 2020, 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 1, sentence 2 VerfO.

By letter dated 30 November 2020 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 11 March 2021, and the written statement procedure was initiated with publication on the G-BA website on 15 March 2021. The deadline for submitting written statements was 6 April 2021.

The oral hearing was held on 26 April 2021.

By letter dated 27 April 2021, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 12 May 2021.

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 assessment of the written statements received and the oral hearing were discussed at the session of the subcommittee on 25 May 2021, and the draft resolution was approved.

At its session on 3 June 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	22 December 2020	Determination of the appropriate comparator therapy
Working group Section 35a	20 April 2021	Information on written statement procedures received; preparation of the oral hearing
Subcommittee Medicinal product	26 April 2021 27 April 2021	Conduct of the oral hearing Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	04 May 2021 18 May 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal product	25 May 2021	Final discussion of the draft resolution
Plenum	3 June 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 3 June 2021

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken