Recommendation No. 133/2021
of 3 December 2021
of the President of the Agency for Health Technology Assessment and Tariff System
on the reimbursement of Calquence (acalabrutinib) under the drug programme "Treatment of chronic lymphocytic leukaemia (ICD 10: C.91.1)"

The President of the Agency does not recommend the reimbursement of Calquence (acalabrutinib) under the drug programme "Treatment of chronic lymphocytic leukaemia (ICD 10: C.91.1)" [information protected as a trade secret] as proposed in the application.

The President of the Agency recommends the reimbursement of Calquence (acalabrutinib) under the drug programme "Treatment of chronic lymphocytic leukaemia (ICD 10: C.91.1)" [information protected as a trade secret] in a new limit group and dispensing free of charge provided that an additional mechanism is proposed to secure payer's budget by setting a maximum ceiling for payer's expenditure on the proposed medicinal product.

Grounds for the recommendation

In the presented analyses, the applicant indicated the following products as comparators for acalabrutinib (AKA):

- in the first-line treatment:
  - obinutuzumab + chlorambucil (OBI+CHB);
  - bendamustine + rituximab (B+R);
  - rituximab + chlorambucil (R+CHB);
  - fludarabine + cyclophosphamide + rituximab (FCR);
- in the second-line treatment of refractory or relapsed chronic lymphocytic leukaemia (CLL):
  - ibrutinib (IBR);
  - venetoclax + rituximab (WEN+R).

<u>First line - AKA vs OBI+CHB</u>

The study revealed no statistically significant differences with regard to:

- Overall survival (OS);

- response to treatment (partial response with lymphoid nodules in general population; stable disease in general population;
- complete response with incomplete haematological recovery;
- overall response to treatment: in general population; [information protected as a trade secret]

Additionally, the administration of AKA vs OBI+CHB was associated with a statistically significantly lower efficacy in achieving complete response in the general population, with 1 patient out of 179 achieving complete response in the study group and 8 out of 177 in the comparator group.

In contrast, AKA vs OBI+CHB was found to be associated with a statistically significant prolongation of progression-free survival (PFS) as assessed by the Independent Response] Review Committee [information protected as a trade secret] in the general population [information protected as a trade secret] The median PFS for the intervention arm was not reached in both the shorter (28.3 months) and longer (46.9 months) follow-up periods, whereas in the control group the median amounted to 22.6 months and 27.8 months respectively.

First line - other comparators

Due to the lack of direct studies comparing AKA with other comparators in the first line, network meta-analysis was performed using common comparators.

AKA vs CHB+R

According to the results of the network meta-analysis, the superiority of AKA over CHB+R was proven in terms of overall survival; progression-free survival ([information protected as a trade secret] general population), overall response to treatment.

Taking this efficacy into account, the estimated ICUR amounted to [information protected as a trade secret] PLN/QALY without the RSS and [information protected as a trade secret] PLN/QALY with the RSS.

AKA vs B+R

According to the results of the network meta-analysis, the superiority of AKA over B+R was proven in terms of progression-free survival ([information protected as a trade secret]; general population). However, no statistically significant differences were observed for overall survival, overall response to treatment.

Taking this efficacy into account, the estimated ICUR amounted to [information protected as a trade secret] PLN/QALY without the RSS and [information protected as a trade secret] PLN/QALY when the RSS is considered.

AKA vs FCR

According to the results of the network meta-analysis, the superiority of AKA over FCR was proven in terms of progression-free survival (in the general population [information protected as a trade secret]. However, no statistically significant differences were observed for overall survival, overall response to treatment.

Taking this efficacy into account, the estimated ICUR amounted to [information protected as a trade secret] PLN/QALY without the RSS and [information protected as a trade secret] PLN/QALY when the RSS is considered.

≥Second line - AKA vs IBR

According to the results of the study in which the two therapies were directly compared, there were no statistically significant differences in overall survival or progression-free survival.

According to the applicant's estimations, in the assumed one-year horizon, treatment with acalabrutinib is [information protected as a trade secret] in the variant including the proposed RSS

and [information protected as a trade secret] in the variant without the RSS.

≥Second line - AKA vs WEN+R

Due to the lack of direct studies evaluating treatment with AKA vs WEN+R, it was decided to conduct the network meta-analysis. The comparison revealed no statistically significant differences in overall survival; progression-free survival; overall response to treatment.

The results of the applicant's cost-minimisation analysis indicate that, taking into account the proposed the RSS, the cost of a single patient-therapy with acalabrutinib is [information protected as a trade secret]

Budget impact

The results of the applicant's budget impact analysis indicate that in the event of a positive decision on the reimbursement of Calquence under the drug programme in question, [information protected as a trade secret]

Limitations of the analyses

When interpreting the aforementioned results, it should be borne in mind that, for reasons of data availability, the analysis of efficacy and safety in the first-line treatment was performed among a broader population than the one that is covered by the application. [information protected as a trade secret] Simultaneously, in refractory/relapsed CLL, the population of the ELEVATE- RR study does not include the full population of patients who will be eligible for treatment under the drug programme in question [information protected as a trade secret]

On 1 November 2021, i.e. after the date of the application submission, the venetoclax + obinutuzumab (WEN+OBI) scheme started to be reimbursed in first-line CLL treatment (regardless of 17p deletion and/or *TP53* gene mutation status).

However, a limitation of the economic analysis is the uncertainty of the data from the main clinical study (ELEVATE-TN) on which the economic analysis model was based. The applicant considered the overall survival data from that study to be insufficiently reliable and instead determined overall survival as the sum of progression-free survival times and survival times after progression by combining data (pooled analysis) from the ELEVATE-TN study with data from the ASCEND study, which was conducted in a population that does not meet the inclusion criteria for CUA, i.e. in patients with refractory/relapsed CLL.

What is more, the model did not employ data from the longer follow-up period of the ELEVATE- TN study (with a median follow-up of 47 months), which were published after the date of the analysis. These data were employed only to validate the adopted assumptions.

One of the limitations of the conducted budget impact analysis is the fact that the prediction of the market structure, both in the new and existing scenario, was based on the opinion of two clinical experts, which may be associated with uncertainty. In addition, the applicant did not take into account the acquisition of market shares in the first-line treatment from the scheme containing high-dose methylprednisolone + rituximab (HDMP + R), which is reimbursed and recommended by Polish clinical guidelines as one of the options of first-line therapy for patients with CLL [information protected as a trade secret] in the absence of targeted therapies.

HTA Agency recommendations include a negative recommendation from IQWIG, a negative recommendation for first line and a positive recommendation for second line PBAC and HAS, a positive recommendation from CADTH, SMC and NICE.

With regard to the position of the Council, clinical guidelines and [information protected as a trade secret], the President of the Agency considers [information protected as a trade secret] provided that [information protected as a trade secret] provided that an additional mechanism would be proposed to secure payer's budget by setting a maximum ceiling for payer's expenditure on the medicinal product in question.

Subject of the application

The order of the Minister of Health concerns the assessment of the appropriateness of public financing of Calquence, acalabrutinib, hard capsules, 100 mg, 60 capsules, GTIN code 05000456061698, for which the proposed net sales price is [information protected as a trade secret]

Proposed payment and dispensing category: free of charge, the drug is to be applied under the drug programme as part of a new limit group. The applicant has submitted a proposal for a risk-sharing scheme.

Health problem

Chronic lymphocytic leukaemia (CLL; ICD-10 code C91.1) is a neoplastic disease of morphologically mature lymphocytes found in the blood, bone marrow, lymphoid tissue and other organs. It is the most common form of leukaemia in Europe and North America. The annual incidence amounts to ~5/100,000 and increases with age - for the age of >60 years, it is ~20/100,000.

The natural history of CLL is highly variable. In most cases, after a phase of a mild history, the disease terminates with a period of severe complications and death (after 5-10 years). The mild history, with a survival time of 10-20 years, in which deaths are usually related to CLL progression or infection, occurs in < 30% of patients. In some patients, the disease develops aggressively from the beginning and leads to death within 2-3 years.

The most common cause of death in CLL is infection (~50% of patients), usually pneumonia and sepsis; other causes include haemorrhage and cachexia. CLL patients present a 2-7 times higher risk of developing another malignant neoplasm than the general population.

Alternative health technology

Considering clinical guidelines and technologies currently publicly funded, the following comparators should be considered:

- in the first-line treatment:
    - obinutuzumab + chlorambucil (OBI+CHB);
    - bendamustine + rituximab (B+R);
    - rituximab + chlorambucil (R+CHB);
    - fludarabine + cyclophosphamide + rituximab (FCR);
- in the second-line treatment of refractory or relapsed chronic lymphocytic leukaemia (CLL):
    - ibrutinib (IBR);
    - venetoclax + rituximab (WEN+R).

In addition, two comparators that the applicant did not consider should be pointed out:

- cladribine + cyclophosphamide + rituximab (CCR);
- high-dose methylprednisolone + rituximab (HDMP+R).

The applicant justified its decision not to select the HDMP+R scheme as a comparator by the fact that the latest European clinical practice guidelines (ESMO 2020, DGHO 2020, HOVON 2020, FILO 2020, GELLC 2020) do not indicate that the HDMP + rituximab scheme can be administered to CLL patients. This scheme is indicated in the Polish clinical practice guidelines (PTHiT_PALG-CLL 2021, PTOK 2020) as an option for first-line treatment of CLL patients, [information protected as a trade secret] due to the lack of reimbursement of BCR and BCL2 inhibitors in Polish conditions. The applicant also pointed out that the CCR scheme is described only in Polish clinical practice guidelines and, additionally, its application is regarded as equivalent (interchangeable) with the FCR scheme.

Neither was the venetoclax + binutuzumab (WEN+OBI) scheme, reimbursed since 1 November 2021 (i.e. after the date of submission of the reimbursement application) in first-line CLL treatment

(irrespective of the 17p deletion status and/or mutation in the *TP53* gene).

Description of the proposed intervention

Acalabrutinib is a selective Bruton tyrosine kinase (BTK) inhibitor. BTK is a signalling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. In B lymphocytes, BTK signalling leads to B-cell survival and proliferation and is required for cell adhesion, cellular transport and chemotaxis.

Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with the cysteine residue in the BTK active site, leading to irreversible inactivation of BTK with minimal off-target interactions.

According to the Summary of Product Characteristics (SmPC), Calquence is indicated for use

- as monotherapy or in combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia;
- as monotherapy for the treatment of adult patients with chronic lymphocytic leukaemia who have received at least one prior therapy.

According to the drug programme covered by the application, Calquence in the first-line treatment [information protected as a trade secret]

[information protected as a trade secret] In refractory/relapsed CLL, the administration of acalabrutinib [information protected as a trade secret]

Efficacy, effectiveness and safety assessment

This assessment involves collecting data on the health consequences (efficacy and safety) of the new therapy for the health problem in question and of other therapies that are currently reimbursed from public funds and represent alternative therapies available for the health problem. Furthermore, this assessment requires determination of the reliability of data collected and a comparison of the efficacy and safety results of the new therapy against the therapies already available to treat the health problem in question.

On the basis of the above, the efficacy and safety assessment allows answering the question of the scale of the health outcome (both in terms of efficacy and safety) to be expected from the new therapy compared with other therapeutic options under consideration.

The clinical and economic analysis was mainly based on:

- ELEVATE-TN - randomised phase III study comparing AKA vs OBI+CHB. In the study, 179 patients received AKA monotherapy and 177 patients received OBI+CHB. The follow-up period was:
    - 28.3 months (data from the full-text publication);
    - 46.9 months (data from conference reports)
- ELEVATE-RR - randomised phase III study comparing AKA vs IBR. The study included 533 patients (AKA group: 268; IBR group: 265). The follow-up period was 40.9 months.

In addition, to compare the proposed technology with the other comparators, the clinical analysis involved:

- 8 studies allowing an indirect comparison of AKA with other comparators:
    - Ibrutinib vs chlorambucil - RESONATE-2 (4 publications: Barr 2018, Burger 2020, Burger 2015, Coutre 2018);
    - Bendamustine + rituximab vs chlorambucil + rituximab - MaBLe (1 publication: Michallet 2018);

- Ibrutinib + rituximab vs fludarabine + cyclophosphamide + rituximab - E1912 (1 publication: Shanafelt 2019);
- Ibrutinib or ibrutinib + rituximab vs bendamustine + rituximab - ALLIANCE (1 publication: Woyach 2018);
- Fludarabine + cyclophosphamide vs chlorambucil - LRF CLL4 (7 publications: Blakemore 2020, Catovsky 2007, Dearden 2008, Else 2016, Gonzalez 2011, Matutes 2013, Oscier 2010)
- Fludarabine + cyclophosphamide + rituximab vs fludarabine + cyclophosphamide - CLL8 (4 publications: Fischer 2016, Gobbi 2009, Hallek 2010 and Kutsch 2017);
- Bendamustine + rituximab vs fludarabine + cyclophosphamide + rituximab - CLL10 (2 publications: Eichhorst 2016 and Kutsch 2020);
- Chlorambucil + obinutuzumab vs chlorambucil vs chlorambucil + rituximab - CLL11 (2 publications: Goede 2014, Goede 2015);

- 2 RCTs in the refractory/relapsed CLL patient population allowing an indirect comparison of AKA vs WEN+R:
  - AKA vs Bendamustine+Rituximab - ASCEND (1 publication: Ghia 2020)
  - venetoclax + rituximab vs bendamustine + rituximab - MURANO (3 publications: Kater 2019, Kater 2020, Seymour 2018).

As assessed by the Cochrane Collaboration recommendations, the ELEVATE-TN and ELEVATE-RR studies have a low risk of bias in most of the domains assessed. Both studies were unblinded; however, when evaluating objective events (such as overall survival) or evaluating an endpoint by the blinded Independent Response Review Committee, the risk of bias was considered low.

Efficacy

<u>First line - AKA vs OBI+CHB</u>

According to the ELEVATE-TN study, the use of AKA vs OBI+CHB was associated with a statistically significantly higher efficacy in terms of:

- progression-free survival (PFS):
  - as assessed by the Independent Response Review Committee:
    - general population, follow-up period of 46.9 months - in the study group the median was not reached, in the control group it was 27.8 months - HR=0.19 (95%CI: 0.13; 0.28);
    - general population, follow-up period of 28.3 months - in the study group the median was not reached, in the control group it was 22.6 months - HR=0.20 (95%CI: 0.13; 0.30); [information protected as a trade secret]
  - as assessed by the researchers:
    - general population, follow-up period of 46.9 months - in the study group the median was not reached, in the control group it was 27.8 months - HR=0.19 (95%CI: 0.13; 0.28);
    - general population, follow-up period of 28.3 months - in the study group the median was not reached, in the control group it was 27.8 months - HR=0.16 (95%CI: 0.10; 0.27); [information protected as a trade secret]

[information protected as a trade secret]

- response to treatment: [information protected as a trade secret]

- partial response in the general population - RR=1.16 (95% CI: 1.04; 1.30), and NNT=8 (95% CI: 5; 27).

According to the ELEVATE-TN study, the treatment with AKA vs OBI+CHB was associated with a statistically significantly lower efficacy in terms of achieving complete response in the general population - 1/179 (0.6%) vs 8/177 (4.5%) RR=0.12 (95% CI: 0.02; 0.98), and NNT=26 (95% CI: 14; 141).

There were no statistically significant differences for the comparison of AKA vs OBI+CHB in terms of:

- overall survival (OS);
- response to treatment:
  - overall response to treatment:
    - in the general population; [information protected as a trade secret]
  - partial response with lymphoid nodules in the general population;
  - stable disease in the general population;
  - complete response with incomplete haematological recovery;

The *Walker 2021*conference report presented information on endpoints assessed by the patient, in which such assessment was performed using the FACIT-Fatigue Global Fatigue Score (GFS) questionnaire (scale 0-52, a lower value indicates more fatigue, clinically significant improvement ≥+3) and the EORTC QLQ-C30 Global Health Status (GHS) (scale 0-100, a lower value indicates worse quality of life, clinically significant improvement >+8). The assessment was performed in all patients (excluding those with progression) and in patients with severe fatigue initially (GFS score ≤ 34). Severe fatigue was present in 56/157 (36%) patients in the AKA group and in 42/141 (30%) patients in the OBI+CHB group.

In both arms, GFS and GHS improved around week 4. The mean change was numerically higher in the AKA group (the authors did not report the statistical significance of the result) than in the OBI+CHB group at both week 4 and week 96 of the analysis. Greater improvements were observed in patients with initial severe fatigue.

A post-hoc analysis of time to clinically meaningful deterioration (*TTD*, change ≤-3) in the GFS score was also performed. The median time to clinically meaningful deterioration on the GFS scale was statistically significantly longer during AKA monotherapy (16.9 months) compared with OBI+CHB (5.7 months).

<u>First line - AKA vs. other comparators (network meta-analysis)</u>

According to the results of the network meta-analysis, AKA was proved to be superior to the other comparators in terms of:

- overall survival **compared to CHB+R**- HR=0.39 (95% CI: 0.16; 0.96);
- progression-free survival:
  - AKA vs CHB+R: [information protected as a trade secret]
    [information protected as a trade secret]
    - general population - HR=0.08 (95% CI: 0.05; 0.13);
  - AKA vs B+R: [information protected as a trade secret]
    - general population - HR=0.08 (95% CI: 0.05; 0.13);
  - AKA vs FCR: [information protected as a trade secret]
    - general population - HR=0.17 (95% CI: 0.10; 0.30).

- overall response to treatment:
    - AKA vs CHB+R:
        - general population - HR=2.75 (95% CI: 1.39; 5.47);

The network meta-analysis demonstrated no statistically significant differences for the use of AKA in terms of:

- overall survival vs: AKA vs B+R; AKA vs FCR; [information protected as a trade secret]
- overall response to treatment: AKA vs B+R; AKA vs FCR.

≥Second line - AKA vs IBR

According to the results of the ELEVATE-RR study, the administration of AKA vs IBR revealed no differences in terms of:

- overall survival;
- progression-free survival.

≥Second line - AKA vs WEN+R (network meta-analysis)

The network meta-analysis demonstrated no statistically significant differences for AKA vs WEN+R administration in terms of:

- Overall survival;
- Progression-free survival;
- Overall response to treatment.

Safety

First line - AKA vs OBI+CHB

Twelve deaths were reported in the AKA group (7% of the patients) and 15 deaths in the OBI+CHB group (9% of the patients). The most common cause of death in both groups was adverse events, which occurred in 3.4% of the patients in the AKA group and 6.5% of the patients in the OBI+CHB group.

The AKA group demonstrated a statistically significantly higher risk of serious adverse events than the OBI+CHB group:

- Overall - RR=1.45 (95% CI: 1.02; 2.08), and NNH=11 (95% CI: 6; 142);
- Grade ≥3 - RR=1.52 (95% CI: 1.04; 2.22), and NNH=10 (95% CI: 6; 90).

Among individual adverse events, a statistically significantly higher risk compared to the OBI+CHB group was observed for bleeding, infection, headache, diarrhoea, injury, joint pain, cough, upper respiratory tract infection, urinary tract infection and rash.

Concurrently, the AKA group presented a statistically significantly lower risk of adverse events compared to the OBI+CHB group:

- Overall adverse events - RR=0.96 (95% CI: 0.93; 1.00), and NNT=27 (95% CI: 14; 397);
- Grade ≥3 adverse events - RR=0.71 (95% CI: 0.60; 0.85), and NNT=5 (95% CI: 4; 10).

Among individual adverse events, a statistically significantly lower risks than in the OBI+CHB group were observed for: tumour breakdown syndrome, neutropenia, infusion-related reactions, fever and thrombocytopenia.

For the remaining adverse events, no statistically significant differences were observed between the study groups.

First line - AKA vs. other comparators (network meta-analysis)

The network meta-analysis revealed that AKA administration was associated with a statistically significantly higher risk of serious adverse events overall than in the CHB+R group (OR=2.29 (95%CI: 1.24; 4.25)) and a statistically significantly lower risk of grade ≥3 neutropenia (OR=0.26 (95%CI: 0.13; 0.51)). For the other endpoints for which the indirect comparison was possible, no differences between the groups were identified. The studies identified in the systematic review did not allow AKA with B+R and with FCR to be compared.

≥Second line - AKA vs IBR

Sixty-two deaths were reported in the AKA group (23% of the patients) and 73 deaths in the IBR group (28% of the patients). The most common cause of death in both groups was adverse events, which occurred in 10.5% of the patients in the AKA group and 12.5% of the patients in the IBR group.

The AKA group was characterised by a statistically significantly lower risk of adverse events leading to treatment discontinuation compared to the IBR group, with RR=0.69 (95% CI: 0.47; 1.00) and NNT=16 (95% CI: 8; 924).

Among individual adverse events, there was a statistically significantly lower risk of the following adverse events compared to the IBR group: atrial fibrillation/flutter, haemorrhage, interstitial lung disease/pneumonia, diarrhoea, joint pain, hypertension, trauma, urinary tract infection, back pain, muscle spasm and digestive disorders.

In contrast, the AKA group demonstrated a statistically significantly higher risk of headache and cough than the IBR group.

For the remaining adverse events, no statistically significant differences were observed between the study groups.

The most common adverse events (>30% of patients) in both groups were diarrhoea and headache.

≥Second line - AKA vs WEN+R (network meta-analysis)

The network meta-analysis showed a statistically significantly lower risk of grade 3-4 neutropenia in the AKA group compared to in the WEN+R group. For the other endpoints for which an indirect comparison was possible, there were no statistically significant differences between AKA and WEN+R.

Limitations

The uncertainty of the presented estimates is affected by the following aspects:

- For reasons of data availability, the analysis of efficacy and safety in first-line treatment was performed in a broader population than that covered in the application. [information protected as a trade secret] No studies were identified to directly compare acalabrutinib with the other comparators used in first-line systemic treatment: R+B, FCR and CHB+R, as well as with WEN+R in refractory/relapsed CLL. Therefore, it was necessary to perform an indirect comparison using the network meta-analysis (NMA) approach, which is inherently of lower reliability;
- In both the ELEVATE-TN and ELEVATE-RR studies, the vast majority of the study population (92.2% in AKA and 94.4% in OBI+CHB and 92.2% in AKA and 91.7% in IBR) were patients with an initial ECOG 0-1 performance status, i.e. relatively good, which may result in a better prognosis. In contrast, patients with the ECOG 0-2 performance status are eligible for the programme;

  ELEVATE-RR study [information protected as a trade secret]

- In the ELEVATE-TN study, the primary endpoint was PFS as assessed by the Independent Response Review Committee for the comparison of the AKA+OBI vs OBI+CHB groups, which

was not the subject of assessment in this procedure;

- The most commonly used prior therapy schemes in the ELEVEATE-RR study were alkylating agents (which include bendamustine, chlorambucil and cyclophosphamide; 90.3% in the AKA group and 90.6% in the IBR group respectively), anti-CD20 monoclonal antibodies (rituximab and obinutuzumab; 84.7% and 86.4% respectively), purine analogues (fludarabine and cladribine; 64.2% and 59.6% respectively) and steroids (23.1% and 23.4% respectively). These schemes coincide with those recommended and currently reimbursed in Poland. It is worth noting, however, that since 1 November 2021, the venetoclax (inhibitor of the anti-apoptotic protein BLC-2) + obinutuzumab scheme has also been publicly funded as first-line CLL treatment (regardless of 17p deletion and/or *TP53* gene mutation). Patients in the ELEVEATE-RR study were not treated with BCL-2 inhibitors prior to AKA, [information protected as a trade secret]
- No studies were identified to compare the quality of life of patients treated with AKA versus comparators other than OBI+CHB. Concurrently, data for the comparison of AKA vs OBI+CHB were derived only from the conference abstract and are unable to demonstrate a difference in efficacy using the MD parameter, thus limiting the possibility to draw conclusions from them;
- The studies identified in the systematic review did not allow a safety analysis for the comparison of AKA with R+R and with FCR;
- An indirect comparison was performed by means of network meta-analysis, which does not allow the results to be verified fully due to the lack of access to the codes involved.

Proposed risk-sharing scheme [information protected as a trade secret]

Economic evaluation, including a cost-effectiveness estimation

Economic evaluation involves estimating and comparing the costs and health outcomes that may be associated with the administration of the new therapy to an individual patient instead of already reimbursed therapies.

The costs of therapy are estimated in Polish currency, and health outcomes are usually expressed in life-years gained (LYG) or quality-adjusted life years (QALY) as a result of the therapy.

Juxtaposing the values concerning the costs and outcomes of a new therapy and comparing them to the costs and outcomes of already reimbursed therapies allows answering the question of whether the health outcome achieved in an individual patient owing to a new therapy is associated with a higher cost in comparison with already reimbursed therapies.

The obtained results of the cost-effectiveness ratio are compared with the so-called cost-effectiveness threshold, i.e. a result that indicates that given the wealth of Poland (expressed in GDP), the maximum cost of the new therapy that is expected to produce a unit of health outcome (1 LYG or 1 QALY) compared to already available therapies should not exceed three times GDP per capita.

Currently, the cost-effectiveness threshold is PLN 166,758 (3 x PLN 55,586).

The cost-effectiveness ratio does not estimate or determine the value of life, but it only enables its assessment and the use of this assessment to choose the therapy associated with the potential best use of the currently available resources.

The purpose of this assessment was to evaluate the cost-effectiveness of Calquence (acalabrutinib) in the treatment of adult patients under the drug programme "Treatment of patients with chronic lymphocytic leukaemia with acalabrutinib (ICD-10 C91.1)" in the first and subsequent lines of treatment. The economic analysis within the first line of treatment in the proposed drug programme was performed with cost-utility analysis (CUA) in a lifetime horizon (30 years), while in the second line of treatment - with cost-minimisation analysis (CMA) in a one-year horizon. The NHF perspective and the joint perspective were considered. Considering the method according to which the drug is financed (i.e. the drug programme), the patient does not pay for the therapy, so the two perspectives

are the same.

The following cost categories were included in the applicant's basic analysis:

- costs of drugs (AKA and comparators),
- costs of diagnosis and therapy monitoring,
- costs of dosage and administration of drugs,
- costs of adverse event treatment,
- cost of treatment after progression,
- cost of terminal care.

CUA

According to the applicant's estimates, the estimated ICUR amounted to:

- AKA vs CHB+OBI:
  - [information protected as a trade secret] PLN/QALY without the RSS;
  - [information protected as a trade secret] PLN/QALY including the RSS;
- AKA vs CHB+R:
  - [information protected as a trade secret] PLN/QALY without the RSS;
  - [information protected as a trade secret] PLN/QALY including the RSS;
- AKA vs B+R:
  - [information protected as a trade secret] PLN/QALY without the RSS;
  - [information protected as a trade secret] PLN/QALY including the RSS;
- AKA vs FCR:
  - [information protected as a trade secret] PLN/QALY without the RSS;
  - [information protected as a trade secret] PLN/QALY including the RSS.

Considering the above ICUR values, the threshold price is: [information protected as a trade secret]

According to the one-way sensitivity analysis, none of the scenarios tested led to a change in the conclusion - [information protected as a trade secret] The largest change in the incremental result relative to the result in the basic analysis ([information protected as a trade secret]) occurred when taking into account:

- change in primary data source for extrapolation of post-progression survival (PPS) to the ELEVATE-TN study ([information protected as a trade secret] relative to the basic analysis);
- the upper scope of the confidence interval for utility values (until progression and after progression) from the basic analysis ([information protected as a trade secret]);
- the lower scope of the confidence interval of the utility values (until progression and after progression) from the basic analysis ([information protected as a trade secret]);

  [information protected as a trade secret]

According to the probabilistic analysis, the probability that acalabrutinib is a cost-effective therapy assuming the applicable cost-effectiveness threshold of PLN 166,758/QALY

CMA

According to the applicant's estimations, in the assumed one-year horizon, treatment with

acalabrutinib is [information protected as a trade secret] in the variant including the proposed RSS and [information protected as a trade secret] in the variant without the RSS. According to the one-way sensitivity analysis [information protected as a trade secret]

In addition, as part of the CMA, the applicant presented a comparison of the proposed intervention to the cost of combination therapy of venetoclax with rituximab among patients with chronic, refractory or relapsed lymphocytic leukaemia. The comparison was performed (unlike the comparison with IBR) over a full patient-therapy horizon, i.e. an AKA treatment length of 38.3 months was adopted (median treatment exposure time in the ELEVATE-RR study) and a WEN+R treatment length of 24.9 months (maximum treatment duration under the B.103 drug programme).

The results of the comparison performed by the applicant indicate that when taking into account the proposed RSS, the cost of a single patient-therapy with acalabrutinib is [information protected as a trade secret]

Limitations

The uncertainty of the presented estimates is affected by the following aspects:

- [information protected as a trade secret] a combined analysis of both acalabrutinib-containing arms of the ELEVATE-TN study (monotherapy arm and combination therapy with obinutuzumab) was performed. The results of the AKA+OBI arm were significantly more favourable than for AKA monotherapy, meaning that the efficacy results of the intervention covered in the application are inflated. In addition, the applicant noted that due to the "immaturity of the results" regarding some endpoints from the ELEVATE-TN studies, results from a longer follow-up period (46.9 months) were used to validate the modelled curves. However, modelling curves based on results from the shorter follow-up period (28.3 months) did not always match results from the longer period ([information protected as a trade secret]).
- due to the lack of access to all data taken for the meta-analysis in the indirect comparison, it was not possible to verify the health outcome data employed in the model ([information protected as a trade secret])
- The assumptions of the analysis did not explain adopting, in the basic scenario, maximum treatment times for therapies within the next line of treatment after disease progression. In particular, the assumption of as many as 220 cycles as ibrutinib treatment time in case of disease progression during OBI+CHB treatment is questionable and results in an overestimation of treatment costs in the comparator arm. The reduction in the length of IBR therapy tested in the sensitivity analysis (to 35.5 cycles) led to [information protected as a trade secret] in the case of the other comparisons.
- The progression-free survival results were modelled through direct access to patient-level data from the ELEVATE-TN study by the global model authors, which makes it difficult to verify the validity of these assumptions.
- For a part of the modelled data (probability of patients progressing from a "pre-progression" state to a "patient death" state), the survival curve in the model overlaps with the survival curve in the general population due to low mortality obtained from prognosis with the parametric model.
- The higher incidence of atrial fibrillation among acalabrutinib-treated patients compared to comparators was not taken into account when considering the cost of treating adverse events in the CUA.
- Utility values of health states were provided based on the social preferences of the general population of the UK, on the basis of value sets developed for the NICE.

Agency's own calculations

In connection with the publication of new NHF data on the average cost of settlement of selected active substances used in drug and chemotherapy programmes for the period from January 2018 to August 2021, (Communication of the Department of Drug Administration of 28 October 2021), the Agency's analysts performed their own calculations of the CUA taking into account the new cost data for rituximab and bendamustine.

All ICUR values (both in the variant with and without RSS) for the AKA comparison with included comparators increased compared to the results of applicant's basic analysis.

In addition, regarding the reimbursement of the venetoclax + obinutuzumab combination therapy under the B.103 drug programme "Treatment of patients with chronic lymphocytic leukaemia with venetoclax (ICD-10: C.91.1)" starting from 1 November 2021, the Agency's analysts decided to present an estimate of the annual costs of administration of acalabrutinib and the WEN+OBI scheme.

As part of the estimates, the dosage of the WEN+OBI scheme and the maximum duration of treatment with this therapy, which is 12 cycles of 28 days each, were adopted according to the B.103 drug programme, where for the first 6 cycles venetoclax is administered together with obinutuzumab, while for the next 6 cycles (from the 7th to the 12th cycle) venetoclax is administered as monotherapy.

The costs of venetoclax and obinutuzumab were calculated based on the tender prices included in applicant's economic analysis model.

When the RSS proposed by the applicant is included, the annual cost of the proposed therapy is [information protected as a trade secret] than the estimated cost of WEN+OBI therapy [information protected as a trade secret], whereas in the variant without the RSS, the cost of acalabrutinib therapy amounts to [information protected as a trade secret] annually. It should be taken into account that the information provided above only includes the costs of individual drugs and omits other costs (administration, diagnosis, adverse events etc.) and health outcomes of both therapies. It should also be noted that the WEN+OBI scheme according to the B.103 drug programme is only used in first-line CLL treatment.

Indication whether the circumstances referred to in Art. 13 sec. 3 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs for particular nutritional uses and medical devices (Dz. U. /Journal of Laws/ of 2021, item 523 as amended) do arise.

If the applicant's clinical analysis does not include randomised clinical trials proving the superiority of the drug over health technologies already reimbursed, the official selling price of the drug must be calculated so that the cost of the drug to be reimbursed is not higher than the cost of the health technology with the most favourable cost–effectiveness ratio.

The applicant presented the randomised trial proving the superiority of AKA vs CHB+OBI in the first-line treatment of CLL, so the circumstances referred to in Art. 13 of the Act on Reimbursement do not arise.

In connection with the lack of randomised clinical trials proving the superiority of the applied technology over the comparator among patients with refractory/relapsed CLL, the circumstances referred to in Art. 13 sec. 3 of the Reimbursement Act arise.

The official selling price of Calquence at which the cost of its use is not higher than the cost of using the optional reimbursed technology with the most favourable cost-effectiveness ratio, i.e. ibrutinib, is [information protected as a trade secret]. For comparison with the WEN+R scheme, the threshold price amounted to [information protected as a trade secret].

Assessment of the impact on the healthcare system, including the budget impact

Healthcare system impact assessment has two major parts.

First, the analysis of the impact on the payer's budget allows estimating the potential expenses associated with public reimbursement of the new therapy.

Estimates of the expenses associated with the new therapy (the "tomorrow" scenario) are compared

to how much is currently spent on treating the health problem (the "today" scenario). On this basis, it is possible to assess whether a new therapy will require more resources allocated to the treatment of the given health problem or whether it will result in savings in the payer's budget.

The budget impact assessment makes it possible to establish whether the payer has adequate resources to fund a particular technology.

Healthcare system impact assessment in the second part answers the question of how the decision on the reimbursement of a new therapy may affect the organisation of the provision of services (particularly in terms of adaptation to the requirements of the implementation of the new therapy) and the availability of other healthcare services.

The budget impact analysis in the event of a positive decision on the reimbursement of Calquence (acalabrutinib) under the proposed drug programme "Treatment of patients with chronic lymphocytic leukaemia with acalabrutinib (ICD-10 C91.1)" was conducted in a 2-year horizon from the public payer perspective and the joint perspective (public payer + patient). Due to the marginal cost on the patient side, the estimate from the joint perspective differs slightly from the patient perspective.

The following cost categories were included in the analysis:

- drug costs (AKA, schemes: FCR, BR, OBI+CHB, CHB+R and IBR, WEN+R);
- drug administration costs;
- cost of diagnosis and monitoring, including the cost of atrial fibrillation diagnosis (the cost of a single diagnostic hospitalisation was included only for acalabrutinib and ibrutinib in refractory/recurrent CLL, in line with the results of the ELEVATE-RR study). [information protected as a trade secret]

According to the applicant's estimates, if Calquence (acalabrutinib) was to be reimbursed as proposed in the application, the expenditure from the payer's perspective [information protected as a trade secret]: [information protected as a trade secret]

Limitations

The uncertainty of the presented estimates is affected by the following aspects:

- Forecasting the market structure, both in the new and existing scenario, was based on the opinion of two clinical experts, which may be associated with uncertainty.
- The applicant did not take into account the acquisition of market shares in the first-line treatment from the HDMP + rituximab scheme, justifying it by the lack of indication of this scheme by the two interviewed clinical experts and current European guidelines, e.g. ESMO. However, this scheme is reimbursed and recommended by the PTHiT PALG-CLL 2021 and PTOK 2020 Polish clinical guidelines as one of the first-line therapy options for patients with CLL [information protected as a trade secret] in the absence of targeted therapies. Moreover, it is worth pointing out that since November 2021, pursuant to the Announcement of the Minister of Health of 21 October 2021, the WEN+OBI scheme in the first line of CLL treatment has been reimbursed, which may affect differences between the market structure projected by the applicant and the actual one. This scheme was not considered in the estimates by the applicant because it started to be reimbursed after the date of submission of the reimbursement application.
  The basis for estimating the size of the target population with refractory/relapsed CLL [information protected as a trade secret]

Agency's own calculations

The Agency's analysts performed additional calculations taking into account the current data presented in the Communication of the Department of Drug Administration of 28 October 2021 on

the average cost of settlement of selected active substances used in drug programmes and chemotherapy for the period from January 2018 to August 2021, according to which the price per 1 mg of rituximab and bendamustine was updated (variant with the RSS). The cost of these substances per 1 mg in August 2021 amounted to PLN 3.31 and PLN 2.18 respectively, which implies a reduction in costs by PLN 0.51 and PLN 0.09 respectively compared to the values (PLN 3.82 and PLN 2.268) adopted in the applicant's analysis.

Taking the costs of rituximab and bendamustine from the Communication of the Department of Drug Administration of 28 October 2021 results in [information protected as a trade secret]).

Comments on the proposed risk-sharing scheme [information protected as a trade secret]

Comments on the drug programme

No remarks.

Discussion on the solutions proposed in the rationalisation analysis

The subject of the rationalisation analysis is the identification of a mechanism, the introduction of which will result in the release of public funds in an amount corresponding to at least the increase in costs resulting from a positive decision on the reimbursement of the health technology covered in this recommendation.

[information protected as a trade secret]

Overview of recommendations in relation to the assessed technology

Five clinical guidelines on chronic lymphocytic leukaemia were identified:

- Polish Society of Haematologists and Transfusiologists, Polish Adult Leukemia Group-CLL (PTHiT PALG-CLL) 2021;
- Polish Society of Clinical Oncology (PTOK) 2020;
- National Comprehensive Cancer Network (NCCN) 2021;
- National Institute for Health and Care Excellence (NICE) 2021;
- European Society for Medical Oncology (ESMO) 2020.

Acalabrutinib therapy is recommended by the PTHiT PALG-CLL 2021, NCCN 2021, NICE 2021 and ESMO 2020 guidelines for first-line treatment of CLL, [information protected as a trade secret]. The NCCN 2021 guidelines recommend both AKA monotherapy and its use in combination with obinutuzumab. In the context of relapsed/refractory CLL treatment, all recommendations identified advise the administration of AKA both in patients with and without the TP53 mutation / 17p deletion.

The Polish PTOK 2020 guidelines do not refer to the use of acalabrutinib, but it should be noted that they were issued before the drug was approved by the European Medicines Agency (EMA).

The most commonly recommended treatment schemes for CLL patients according to the guidelines identified, with the highest recommendation strength, are:

- as part of first-line treatment:
    - in patients with the TP53 mutation / 17p deletion: acalabrutinib ± obinutuzumab, ibrutinib ± rituximab, idelalisib ± rituximab, venetoclax ± obinutuzumab. When lacking access to the new treatment methods, therapeutic options include: FCR/CCR schemes, BR, HDMP + rituximab, chlorambucil ± obinutuzumab, alemtuzumab + methylprednisolone/± rituximab, RCD;
    - in patients without the TP53 mutation / 17p deletion and non-mutated IGHV gene: ibrutinib, acalabrutinib, alternatives: venetoclax + obinutuzumab. When lacking access to the new treatment methods, therapeutic options include:

immunochemotherapy: FCR/CCR, BR (if patients are in good general condition, without significant comorbidities) and obinutuzumab + chlorambucil (if patients are in worse general condition, with comorbidities).

- subsequent lines of treatment: acalabrutinib, ibrutinib, idelalisib + rituximab, venetoclax ± rituximab. When lacking access to the new treatment methods, other therapeutic options include FCR/CCR, BR, HDMP + rituximab.

Reimbursement recommendations from 7 agencies have been identified:

NICE 2021 - Akalabrutinib is recommended in monotherapy as a treatment option for adults with previously untreated chronic lymphocytic leukaemia, [information protected as a trade secret]

- Haute Autorite de Sante (HAS) 2021:
    - The HAS Committee recommends acalabrutinib in:
        - First-line treatment of CLL in combination with obinutuzumab or in monotherapy: [information protected as a trade secret]
        - ≥2 lines of treatment in monotherapy provided there is no 17p deletion or TP53 mutation in the patient.
    - The HAS Committee does not recommend acalabrutinib in:
        - First-line treatment in combination with obinutuzumab or in monotherapy [information protected as a trade secret]
        - Second-line treatment in monotherapy, [information protected as a trade secret]
- The Scottish Medicines Consortium (SMC) 2021 recommends acalabrutinib in:
    - monotherapy for the treatment of CLL patients previously receiving ≥ 1 line of treatment, [information protected as a trade secret]

      monotherapy or in combination with obinutuzumab in patients with previously untreated CLL, [information protected as a trade secret]

      monotherapy in the treatment of adult patients with previously untreated CLL [information protected as a trade secret]
- Canadian Agency for Drugs and Technologies in Health (CADTH):
    - 2021 recommendation - the CADTH Canadian Drug Expert Committee (CDEC) recommends funding acalabrutinib as monotherapy in patients with previously untreated chronic lymphocytic leukaemia, [information protected as a trade secret] provided that the cost-effectiveness is raised an acceptable level, which would improve the probability that it is a cost-effective treatment;
    - 2020 recommendation - the CADTH Canadian Drug Expert Committee (CDEC) recommends acalabrutinib in monotherapy for the treatment of adults with active, refractory or relapsed chronic lymphocytic leukaemia previously receiving ≥1 line of treatment provided that the cost-effectiveness of the therapy is modified. Treatment with acalabrutinib should be continued until disease progression or unacceptable toxicity.
- IQWIG 2021a - the German IQWIG Committee does not recommend acalabrutinib:
    - in the treatment of previously untreated CLL patients: [information protected as a

trade secret]

- in the treatment of previously treated CLL patients: [information protected as a trade secret]

- National Centre for Pharmacoeconomics (NCPE) 2021 – the NCPE Committee does not recommend acalabrutinib in the indications:
  - in monotherapy for the treatment of CLL patients previously receiving ≥ 1 line of treatment; in monotherapy for the treatment of patients previously untreated [information protected as a trade secret]

- Pharmaceutical Benefits Advisory Committee (PBAC):
  - 2020a recommendation - the Committee recommends acalabrutinib for the treatment of patients with refractory or relapsed CLL not eligible for subsequent treatment with purine analogues;
  - 2020b recommendation - the Committee does not recommend acalabrutinib in monotherapy or in combination with obinutuzumab for the treatment of patients with CLL previously untreated, ineligible for purine analogue therapy or, [information protected as a trade secret]

Legal basis for the recommendation

The recommendation was prepared based on the order of the Minister of Health of 20 September 2021 (ref. no.: PLR.4500.1428.2021.15.APR) concerning the preparation of the President's recommendation on the reimbursement of Calquence (acalabrutinib) under the drug programme "Treatment of chronic lymphocytic leukaemia (ICD-10: C91.1)" pursuant to Art. 35 sec. 1 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs intended for particular nutritional uses and medical devices (Dz. U. /Journal of Laws/ of 2021, item 523 as amended), having obtained Position of the Transparency Council No. 133/2021 of 29 November 2021 on the assessment of Calquence (acalabrutinib) under the drug programme ''Treatment of chronic lymphocytic leukaemia (ICD-10: C91.1)''.

References

1. Position of the Transparency Council No. 133/2021 of 29 November 2021 on the assessment of Calquence (acalabrutinib) under the drug programme ''Treatment of chronic lymphocytic leukaemia (ICD-10: C91.1)''
2. Report No. OT.4231.45.2021. "Application for the reimbursement of Calquence (acalabrutinib) under the drug programme ''Treatment of chronic lymphocytic leukaemia (ICD-10: C91.1)''. Verification analysis