NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Acalabrutinib for treating chronic lymphocytic leukaemia

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using acalabrutinib in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: December 2020

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using acalabrutinib in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: Monday 11 January 2021

Second appraisal committee meeting: To be confirmed

Details of membership of the appraisal committee are given in section X

1 Recommendations

1.1 Acalabrutinib is recommended as an option for untreated chronic lymphocytic leukaemia (CLL) in adults, only if:

- they have a 17p deletion or TP53 mutation and
- the company provides it according to the commercial arrangement (see section 2).

1.2 Acalabrutinib is recommended as an option for treating CLL in adults who have had at least 1 previous treatment, only if:

- ibrutinib is their only suitable treatment option, and
- the company provides it according to the commercial arrangement (see section 2).

1.3 These recommendations are not intended to affect treatment with acalabrutinib that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

People with untreated CLL and a 17p deletion or TP53 mutation usually have ibrutinib. For this group, acalabrutinib has not been directly compared with ibrutinib in a clinical trial, and the results of an indirect comparison are uncertain. The company assumed that acalabrutinib is equally effective as ibrutinib in a cost-minimisation analysis. Despite the uncertainties, acalabrutinib is likely to be cost-saving compared with ibrutinib. So acalabrutinib is recommended for routine use in the NHS for this group.

People with untreated CLL without a 17p deletion or TP53 mutation usually have fludarabine, cyclophosphamide and rituximab (FCR) or bendamustine plus rituximab (BR). If FCR or BR is unsuitable, chlorambucil plus obinutuzumab is offered instead.

Issue date: December 2020

For the group when FCR or BR is unsuitable, clinical trial evidence shows that CLL treated with acalabrutinib therapy takes longer to progress than CLL treated with chlorambucil plus obinutuzumab. However, the overall survival benefit is uncertain. The cost-effectiveness estimates are higher than what NICE normally considers acceptable, so acalabrutinib cannot be recommended for routine use in the NHS for this group. Acalabrutinib does not meet the criteria to be included in the Cancer Drugs Fund.

People with previously treated CLL whose disease has relapsed or does not respond to treatment usually have ibrutinib or venetoclax plus rituximab. For this group, acalabrutinib has not been directly compared with ibrutinib or with venetoclax plus rituximab in a clinical trial. The results of an indirect comparison with ibrutinib are uncertain. The company assumed that acalabrutinib was equally effective as ibrutinib in the cost-minimisation analyses presented which resulted in acalabrutinib being less costly than ibrutinib. Despite the uncertainty, acalabrutinib is likely to be cost-saving compared with ibrutinib. So acalabrutinib is recommended for routine use in the NHS for people with previously treated CLL. However, because the company did not present any analyses comparing acalabrutinib with venetoclax plus rituximab, it is only recommended if ibrutinib is their only suitable treatment option.

2 Information about acalabrutinib

Anticipated marketing authorisation indication

2.1 Acalabrutinib (Calquence, AstraZeneca) is indicated:

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

The company did not submit evidence to support reimbursement for acalabrutinib in combination with obinutuzumab. It also did not provide evidence for previously untreated adults with CLL who are eligible for fludarabine, cyclophosphamide and rituximab-based (FCR) therapy (see section 3.5).

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 A 30-day pack of acalabrutinib 100 mg tablets costs £5,059. The company has a commercial arrangement (simple discount patient access scheme). This makes acalabrutinib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by AstraZeneca, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Chronic lymphocytic leukaemia has substantial effects on quality of life

3.1 Chronic lymphocytic leukaemia (CLL) is a malignant disorder of white blood cells and is the most common type of leukaemia in England. The patient experts explained that the physical and psychological effects of CLL have a debilitating effect on their daily lives. The committee noted the increase in prevalence of CLL with age and the additional effect of the condition on family and carers. It concluded that CLL substantially affects both physical and psychological aspects of quality of life.

Treatment pathway and comparators

There is an unmet need for more effective treatments for CLL and a new treatment option would be welcomed

3.2 The clinical and patient experts noted that people with untreated CLL are a heterogeneous population, with different mutation status and comorbidities. They agreed that there is an unmet need for more effective, targeted treatments with fewer side effects than existing NHS treatments. They considered that this unmet need is particularly high for people with a 17p deletion or TP53 mutation. This is because ibrutinib and idelalisib plus rituximab are the only available treatments, and idelalisib is poorly tolerated and not widely used. However, for people without a 17p deletion or TP53 mutation there is also a need for greater treatment choice. Around one-third of this population are offered fludarabine, cyclophosphamide and rituximab (FCR) or bendamustine plus rituximab (BR), which have many long-term side effects. The patient experts also noted that access to treatments other than these chemo-immunotherapies is limited. Chlorambucil plus obinutuzumab is the only other option so targeted treatments such as acalabrutinib are needed. The committee acknowledged that for previously treated CLL that has progressed, the treatment options are currently limited to either ibrutinib or venetoclax plus rituximab. The patient experts explained that acalabrutinib is generally well tolerated and causes fewer side effects than current treatments. Also, it is an option when ibrutinib is not suitable for some people with cardiovascular comorbidities. The committee concluded that acalabrutinib would be welcomed as a new treatment option for people with CLL.

Treatment varies depending on mutation status and comorbidities

3.3 The clinical experts confirmed that mutation status and comorbidities affect the treatment options for people with untreated CLL. People without a 17p deletion or TP53 mutation who have comorbidities that make FCR and BR unsuitable for them would be offered chlorambucil plus obinutuzumab. People with a 17p deletion or TP53 mutation would usually

be offered ibrutinib. Idelalisib plus rituximab is rarely used in clinical practice because it has an intensive dosing regimen and is associated with increased infection risk. The clinical experts also stated that ibrutinib is the most commonly used treatment for previously treated CLL that has progressed, but venetoclax plus rituximab is also used. The committee agreed that it was appropriate to model different treatments depending on mutation status and comorbidities.

For previously treated CLL, venetoclax plus rituximab is a relevant comparator

3.4 The company did not present evidence comparing acalabrutinib with venetoclax plus rituximab for the population with previously treated relapsed or refractory CLL. It did not consider venetoclax plus rituximab to be a commonly used treatment in this population in the NHS. Instead, it regarded ibrutinib to be the established treatment for relapsed or refractory CLL in the NHS and was the only comparator in its cost-minimisation analysis for this population. The committee noted that a proportion of this population would likely have venetoclax plus rituximab, but the economic analysis did not include costs for this combination. The committee concluded that although venetoclax plus rituximab was a relevant comparator for previously treated relapsed or refractory CLL, the results of the cost-minimisation analysis only apply when ibrutinib is the only suitable treatment option.

The company does not present any evidence for a population with untreated CLL for whom FCR or BR is suitable

3.5 The company's submission did not include people with untreated CLL for whom FCR or BR is suitable, although this population was in the NICE scope and is included in the anticipated marketing authorisation for acalabrutinib. The patient experts suggested that acalabrutinib should have been presented in the company's submission as an alternative to chemo-immunotherapy for this population. However, the company's clinical experts suggested excluding this population from its clinical trial,

ELEVATE-TN, in line with expected clinical practice. The company explained that ELEVATE-TN did include people with untreated CLL for whom FCR or BR is suitable, but the company presented no clinical or cost evidence for this group. The committee acknowledged that the company was not seeking reimbursement for acalabrutinib for this population and that no comparative evidence was presented. The committee concluded that although people with untreated CLL for whom FCR or BR is suitable is an important subgroup, it could not make a recommendation for this group because no evidence had been presented.

Clinical effectiveness

The clinical effectiveness evidence is largely relevant to NHS clinical practice in England

3.6 The company presented results for the population with untreated CLL from ELEVATE-TN, an open-label randomised controlled trial comparing acalabrutinib monotherapy (n=179) with chlorambucil plus obinutuzumab (n=177). ELEVATE-TN included people over 18 years with untreated CLL whose multimorbidities made FCR or BR unsuitable. People in ELEVATE-TN had to have a Cumulative Illness Rating Scale score greater than 6, or a creatinine clearance of less than 70 ml/min (low creatinine clearance levels indicate serious kidney damage). The company considered that these criteria meant that FCR or BR would be unsuitable for similar patients in NHS clinical practice. ELEVATE-TN also included an acalabrutinib plus obinutuzumab arm but this was not part of the company's submission and was not considered further. Of the 356 people in ELEVATE-TN, 35 had a 17p deletion or TP53 mutation. For the population with previously treated CLL, the company presented clinical effectiveness evidence from ASCEND. This was an open-label randomised controlled trial comparing acalabrutinib (n=155) with either idelalisib plus rituximab or BR (n=155). The ERG considered that the population in ELEVATE-TN broadly represented the population with untreated CLL for whom FCR or BR was unsuitable seen in the NHS in

England. Also, the population in ASCEND broadly represented the population with previously treated relapsed or refractory CLL who would be eligible for treatment with acalabrutinib. The committee was satisfied that the clinical effectiveness evidence was largely relevant to NHS clinical practice.

It is acceptable to use the full trial data from ELEVATE-TN in the untreated CLL model

3.7 The company used data from ELEVATE-TN to inform the economic analysis for the populations with untreated CLL. ELEVATE-TN included 35 people with high-risk CLL, that is, with a 17p deletion or TP53 mutation. The ERG explained that the company's economic model for untreated CLL used the full population from ELEVATE-TN. Because there is a separate model for people with high-risk CLL, this resulted in the same population with high-risk CLL being included in 2 different models with different comparators. The ERG noted that the effect of including the population with high-risk CLL in the untreated CLL model was uncertain. The clinical experts explained that it was reasonable to assume a similar treatment effect of acalabrutinib for the populations with untreated CLL whether or not they had high-risk CLL. They considered that it was therefore acceptable to include both populations in the same model. The committee agreed and concluded that it was acceptable to use the full trial data from ELEVATE-TN in the untreated CLL model.

For untreated CLL when FCR or BR is unsuitable, acalabrutinib improves progression-free survival but the overall survival benefit is uncertain

3.8 After a median follow-up of 28 months, there was a statistically significant increase in progression-free survival for acalabrutinib compared with chlorambucil plus obinutuzumab (hazard ratio [HR] 0.20, 95% confidence interval [CI] 0.13 to 0.30, p<0.0001). Median progression-free survival was not reached in the acalabrutinib arm and was 22.6 months in the chlorambucil plus obinutuzumab arm. Median time to next treatment was

not reached in either treatment arm but the trend was towards this being longer with acalabrutinib. Median overall survival was not reached in either treatment arm and there was no difference in overall survival between the 2 arms (HR 0.60, 95% CI 0.28 to 1.27, p=0.1556). The committee concluded that the trial data showed that acalabrutinib increased progression-free survival and time to next treatment compared with chlorambucil plus obinutuzumab. The committee considered that the benefit of acalabrutinib on overall survival was uncertain, noting the immaturity of the data (that is, the endpoints had not been reached).

For untreated high-risk CLL, an indirect treatment comparison in a different population is used but is acceptable for decision making

3.9 The company's economic model for the population with untreated high-risk CLL used data from an indirect treatment comparison in the population with relapsed or refractory disease (see next section). The company considered that the results from the indirect comparison could apply to the population with high-risk CLL. and that acalabrutinib is clinically equivalent to ibrutinib. The ERG explained that as the data did not specifically relate to this population, there was uncertainty in assuming clinical equivalence based on the separate relapsed or refractory CLL population analysis. The clinical experts explained that there was no reason to consider acalabrutinib to be clinically inferior to ibrutinib and that assuming equivalent effectiveness was reasonable. The committee noted that there was no direct evidence presented for the population with high-risk CLL. Although there was uncertainty, it concluded that it was plausible that clinical equivalence between acalabrutinib and ibrutinib could be assumed in both populations and this was acceptable for decision making.

For previously treated CLL, the company's indirect treatment comparison with ibrutinib is acceptable for decision making

3.10 No direct evidence was presented comparing acalabrutinib with ibrutinib for the population with previously treated relapsed or refractory CLL. The company did an unanchored matching adjusted indirect comparison

(MAIC) using data from the acalabrutinib arm of ASCEND and the ibrutinib arm of RESONATE. Individual patient data were weighted to match baseline characteristics between arms and all observed effect modifiers and prognostic variables accounted for in the analysis. Kaplan–Meier estimates for progression-free survival and overall survival were found to be similar for both interventions (the exact hazard ratios and statistical values are confidential and cannot be reported here). The results of the MAIC were used to inform the cost-minimisation approach for the population with previously treated relapsed or refractory CLL. The company considered that the results justified the assumption of equivalent efficacy between acalabrutinib and ibrutinib in the populations with previously treated relapsed or refractory CLL and untreated high-risk CLL. The ERG considered that the methods for the indirect comparison were appropriate, concluding that it was reasonable to assume clinical equivalence of acalabrutinib and ibrutinib in the population with previously treated relapsed or refractory CLL. The committee concluded that the indirect treatment comparison was acceptable for decision making.

Adverse effects

Acalabrutinib is generally well tolerated compared with current treatments

3.11 The results of ELEVATE-TN showed that acalabrutinib had an acceptable tolerability profile compared with chlorambucil plus obinutuzumab. The patient experts highlighted that acalabrutinib was associated with fewer adverse effects and was generally well tolerated. They explained that some people noted reduced adverse effects after changing to acalabrutinib from other treatments. The committee agreed that acalabrutinib was likely to be generally well tolerated compared with current treatments.

Cost-effectiveness model structure

The model structure is appropriate for decision making

3.12 For the population with untreated CLL, the company submitted a semi-Markov model with 3 states (progression-free, progressed disease and death). The company used data from ELEVATE-TN to estimate progression-free survival, overall survival and time to next treatment using parametric curves fitted to Kaplan–Meier data. Post-progression survival was estimated from the overall survival data from trials in previously treated CLL; MURANO and RESONATE. Data from the venetoclax plus rituximab arm of MURANO were applied to people progressing on first-line acalabrutinib. Data from the ibrutinib arm of RESONATE were applied to people progressing on chlorambucil plus obinutuzumab. Acalabrutinib treatment was assumed to continue until disease progression or death. Chlorambucil plus obinutuzumab was given for 6 cycles or until disease progression or death. Following disease progression after initial treatment, the model included a delay between disease progression and starting subsequent treatment. The ERG highlighted that the model structure did not allow for a second progression event and subsequent treatment costs were applied from the start of the second treatment until death or the maximum treatment duration. The committee noted the uncertainty about the duration of subsequent treatment (see sections 3.13 and 3.14) but concluded that the model structure was appropriate for decision making.

Subsequent treatment

For untreated CLL the distribution of subsequent treatments is uncertain

3.13 In the company's untreated CLL model, it assumed that the type of second-line treatment would depend on their first-line treatment. After disease progression, the company assumed that people in the acalabrutinib group would have second-line treatment with venetoclax plus rituximab and people in the chlorambucil plus obinutuzumab group would have ibrutinib. This sequence was assumed because, in clinical

practice, it is unlikely that people would have a Bruton's Tyrosine Kinase (BTK) inhibitor such as acalabrutinib after another BTK inhibitor such as ibrutinib. The company considered that ibrutinib was mainly used after chlorambucil plus obinutuzumab in the NHS. The company's model accounted for a proportion of people in the chlorambucil plus obinutuzumab group having venetoclax plus rituximab. The ERG highlighted that there was some uncertainty in the proportion of people who would have venetoclax plus rituximab in the chlorambucil plus obinutuzumab group. The clinical experts explained that venetoclax plus rituximab was a relatively recent treatment option. It was likely to account for between 20% and 50% of second-line treatment after chlorambucil plus obinutuzumab and would increase over time. The committee acknowledged that these proportions were substantially higher than those proposed in the company's model and considered scenarios with a range of proportions. The committee agreed that the distribution of subsequent treatments after disease progression in the untreated CLL model was uncertain. It concluded that it was plausible venetoclax plus rituximab would account for at least 20% of second-line treatment after chlorambucil plus obinutuzumab and possibly up to 40%.

For untreated CLL subsequent treatment costs are likely to be overestimated

3.14 In the company's original economic model subsequent treatment and its associated costs were modelled to continue from the start of subsequent treatment until death. However, the ERG highlighted that the model incorrectly applied second-line treatment costs because people would only have second-line treatment until progression. At this point treatment, and costs, would stop. In response to comments submitted by the company as part of their check of the factual accuracy of the ERG report, the ERG developed a second-line treatment costing model. In the ERG's model, mean progression-free survival for second-line ibrutinib treatment was extrapolated from the RESONATE progression-free survival data for

1 to 2 prior lines of treatment. The company agreed with this approach, but disagreed with the ERG on 2 points:

- The company preferred a log-normal parametric curve for second-line treatment duration, which estimated a duration of 5.56 years for ibrutinib treatment. The ERG preferred the Weibull curve, which estimated a duration of 4.78 years.
- The company assumed that the delay from progressing on first-line treatment through to starting second-line treatment would be 1 cycle. But the ERG used the company's original assumption of a 14-cycle delay.

The ERG highlighted that the subsequent treatment costs accounted for a substantial proportion of the overall costs of the chlorambucil plus obinutuzumab comparator group. So increasing the duration of second-line ibrutinib treatment in the chlorambucil plus obinutuzumab group substantially increased the overall costs compared to the acalabrutinib group. The company considered that the log-normal distribution provided the most clinically realistic second-line ibrutinib treatment duration and provided the best statistical fit to the data. The clinical experts suggested that a second-line treatment duration of around 4.5 years for ibrutinib was reasonable, which corresponded to the ERG's approach. The ERG also highlighted that reducing the delay from progression to second-line treatment led to a much greater increase in the subsequent treatment cost of ibrutinib in the chlorambucil plus obinutuzumab group than in the subsequent treatment cost of venetoclax plus rituximab in the acalabrutinib group. The company explained that the 14-cycle delay was included to account for the assumption that patients would have subsequent treatments at different ages depending on when they progressed. The company reduced the delay to 1 cycle because it considered that the ERG's model used a more personalised approach. The company also explained that the 14-cycle delay was based on immature data from ELEVATE-TN. It discussed this with its clinical

advisers who suggested that the 14-cycle delay was not clinically plausible because patients would not have to wait for 1 year before starting second-line treatment. The ERG noted that the company's submission did not clearly identify the rationale for assuming a 14-cycle delay and that data from ELEVATE-TN could be used to determine the mean delay but those data were not presented. The clinical experts explained that in practice it is sometimes reasonable to wait 1 year before starting second-line treatment after progression with chlorambucil plus obinutuzumab. The committee considered the log-normal parametric model to be plausible but preferred the Weibull as it was less constrained by overall survival gains. It noted some uncertainty about the appropriate delay between progression and starting second-line treatment and separate scenarios were considered for the 14-cycle and the 1-cycle delays. The committee also acknowledged the effect of sequencing on costs of subsequent treatments (see section 3.13). It concluded that the costs of subsequent treatments in the chlorambucil plus obinutuzumab group were likely overestimated in the company base case and considered different scenarios in their decision making.

Survival extrapolations

For untreated CLL the overall survival data are immature, leading to highly uncertain survival estimates

3.15 The data from ELEVATE-TN showed a trend towards improved overall survival for acalabrutinib compared with chlorambucil plus obinutuzumab. But the data were immature, with median follow-up at 28 months, and the difference between the groups was not statistically significant. The company estimated overall survival as a function of time to progression, pre-progression mortality and post-progression survival. Parametric survival models were fitted to data from ELEVATE-TN to model time to progression and pre-progression mortality. Post-progression survival in the acalabrutinib arm used overall survival data from the venetoclax plus rituximab arm of the MURANO trial. In the chlorambucil plus

obinutuzumab group, data from the ibrutinib arm of RESONATE were used in a similar way, but resulted in a lower overall survival rate. The ERG considered this approach favoured the sequence using venetoclax plus rituximab but that it was possible the difference in overall survival was because of confounding due to the unadjusted arm-based comparison. The company considered that the MURANO and RESONATE trials reflected clinical practice for subsequent treatments as indicated by its clinical advisers. So it considered the post-progression survival estimates reasonable. The ERG highlighted that when modelling post-progression survival using MURANO, the overall survival hazard converged with that for the general population. This led to most people having acalabrutinib followed by venetoclax plus rituximab having similar survival to the general population. The ERG preferred to assume equal rates of post-progression survival for the acalabrutinib and chlorambucil plus obinutuzumab groups based on post-progression survival data from RESONATE because this leads to less optimistic projections of overall survival. The clinical experts suggested that overall survival was likely to be longer when starting treatment with acalabrutinib followed by venetoclax plus rituximab. This is because it is more effective and less toxic than chlorambucil plus obinutuzumab followed by ibrutinib. However, long-term data confirming overall survival benefit is lacking at present. They considered it reasonable to use MURANO because it accurately reflects the most likely treatment sequence of acalabrutinib followed by venetoclax plus rituximab. The clinical experts also explained that it was reasonable to expect that many people will reach the life expectancy of the general population after treatment with acalabrutinib and will be functionally cured. The committee concluded that there was considerable uncertainty in the overall survival estimates for acalabrutinib because of the extrapolation using data from trials for other treatments and the immature data from ELEVATE-TN.

Cost-effectiveness results

For untreated CLL when FCR or BR is unsuitable, the ICERs are higher than normally considered acceptable

3.16 The ICERs used by the committee for decision-making took account of all available confidential discounts, including those for comparators and follow-up treatments. The company's revised base-case incremental cost-effectiveness ratio (ICER) for acalabrutinib compared with chlorambucil plus obinutuzumab for untreated CLL when FCR or BR is unsuitable was above what would normally be considered cost-effective. Incorporating the ERG's preferred assumptions on applying a 14-cycle delay and using the Weibull model for subsequent treatment (see section 3.14) and using RESONATE post-progression survival for both treatment arms (see section 3.15) increased the ICER considerably. The committee used the ERG's base case for decision making. However, it also considered that further assumptions should be included in that base case:

- The proportion of patients having second-line venetoclax plus rituximab was at least 20%, and possibly up to 40% (see section 3.13)
- Adjusting the overall survival gain for acalabrutinib compared with chlorambucil plus obinutuzumab such that it was 50% lower, reflecting uncertainty about the immature survival data in ELEVATE-TN (see section 3.15)

In all the ERG's scenarios explored by the committee the ICERs remained higher than the range NICE normally considers an acceptable use of NHS resources. Taking the uncertainties in subsequent treatment costs and survival estimates into account, the committee concluded that, in all scenarios, acalabrutinib would not be considered an acceptable use of NHS resources for untreated CLL that is not high risk and when FCR or BR is unsuitable.

For people with a 17p deletion or TP53 mutation, acalabrutinib likely to be cost-saving compared with ibrutinib

3.17 In the company's base case from its cost-minimisation analysis, costs for acalabrutinib were lower than costs for ibrutinib for people with untreated CLL with a 17p deletion or TP53 mutation (high-risk CLL). The cost-minimisation analysis considered whether the acquisition and management of adverse events costs for acalabrutinib were lower than for ibrutinib. The ERG's analysis made no substantial changes to the company's base case and resulted in mostly unchanged cost savings for acalabrutinib treatment. final costs considered by the committee took account of all available confidential discounts, including those for comparators. The committee concluded that for people with untreated CLL with a 17p deletion or TP53 mutation, acalabrutinib is likely to be cost-saving compared with ibrutinib.

For previously treated CLL, acalabrutinib is likely to be cost-saving compared with ibrutinib

3.18 In the company's base case from its cost-minimisation analysis, costs for acalabrutinib were lower than costs for ibrutinib for people with previously treated CLL. The cost-minimisation analysis considered whether the acquisition and management of adverse events costs for acalabrutinib were lower than for ibrutinib. The ERG's analysis made no substantial changes to the company's base case and resulted in mostly unchanged cost savings for acalabrutinib treatment. The final costs considered by the committee took account of all available confidential discounts, including those for comparators. The committee concluded that for people with previously treated CLL acalabrutinib was likely to be cost-saving comparing with ibrutinib. However, the committee considered that venetoclax plus rituximab was a relevant comparator for this population but the company did not present a comparison with acalabrutinib (see section 3.5).

End of life

Acalabrutinib does not meet the criteria to be considered a life-extending treatment at the end of life

3.19 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. It considered that the short life expectancy criterion of less than 24 months was not met because people with CLL have a life expectancy of more than 2 years. The committee concluded that acalabrutinib does not meet the criteria to be considered a life-extending treatment at end of life.

Conclusions

Acalabrutinib is not recommended for untreated CLL that is not high risk and when FCR or BR is unsuitable

3.20 The committee considered the uncertainties with subsequent treatment costs and survival estimates. It concluded that, in all scenarios, the ICERs for acalabrutinib would not be considered an acceptable use of NHS resources for untreated CLL that is not high risk and when FCR or BR is unsuitable (see section 3.16). The committee concluded that acalabrutinib could not be recommended for routine use in the NHS for this population.

Acalabrutinib is recommended for people with a 17p deletion or TP53 mutation

3.21 The committee considered the uncertainty in the evidence for a population with untreated CLL with a 17p deletion or TP53 mutation. However, it considered the economic model to be appropriate for decision making (see section 3.17). The committee concluded that for people with untreated CLL with a 17p deletion or TP53 mutation, acalabrutinib was likely to be cost-saving compared with ibrutinib. So it could be recommended as an option for this population.

Acalabrutinib is recommended for previously treated CLL when ibrutinib is the only suitable treatment option

3.22 The committee considered that venetoclax plus rituximab was a relevant comparator for this population but no evidence comparing it with acalabrutinib was presented (see section 3.18). It concluded that the economic model was appropriate to compare acalabrutinib with ibrutinib and acalabrutinib was likely to be cost-saving compared with ibrutinib. So it could be recommended as an option for previously treated CLL, but only when ibrutinib is the only suitable treatment option.

Cancer Drugs Fund

Acalabrutinib does not meet the criteria for the Cancer Drugs Fund

3.23 Having concluded that acalabrutinib could not be recommended for routine use for untreated CLL when FCR or BR is unsuitable (see section 3.16), the committee then considered if it could be recommended for use within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). The committee considered whether the clinical uncertainty associated with acalabrutinib for this patient population could be addressed by collecting more data. The committee acknowledged that ELEVATE-TN is ongoing. However, given that overall survival could be similar to the general population (see section 3.15), further follow-up within the usual time-frame of the Cancer Drugs Fund was unlikely to resolve the uncertainty. In addition, the committee noted that acalabrutinib was not plausibly cost-effective in any of the scenarios it considered (see section 3.16). So acalabrutinib did not meet the criteria to be considered for inclusion in the Cancer Drugs Fund.

Equality considerations

There are no equality issues relevant to the recommendations

3.24 The company's submission did not include people with untreated CLL for whom FCR or BR is suitable. Patient submissions highlighted that this would potentially deny younger and fitter people access to a new treatment option that is well tolerated. However, the committee could not make a recommendation about the clinical and cost effectiveness of acalabrutinib for this population because the company did not present any evidence. So the committee did not consider this an equality issue it could resolve.

Innovation

There are no additional benefits that are not captured in the QALY calculations

3.25 The company considered acalabrutinib to be an innovative treatment because it is a highly selective BTK inhibitor that addresses a significant unmet need in first-line CLL treatment. Also, it offers an alternative option to the first-generation BTK inhibitor in previously treated CLL. Its targeted mechanism of action means it offers improved safety and tolerability compared with current treatments. The committee concluded that acalabrutinib would be a beneficial additional treatment option. However, it noted that it had not been presented with evidence of any additional benefits that were not captured in the measurement of quality-adjusted life years (QALYs).

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal

within 3 months of its date of publication. Because acalabrutinib has been available through the early access to medicines scheme, NHS England and commissioning groups have agreed to provide funding to implement this guidance 30 days after publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an early access to medicines scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has chronic lymphocytic leukaemia and the doctor responsible for their care thinks that acalabrutinib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Proposed date for review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Stephen O'Brien
Chair, appraisal committee
November 2020

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Issue date: December 2020

Omar Moreea

Technical lead

Richard Diaz

Technical adviser

Louise Jafferally

Project manager

ISBN: [to be added at publication]