NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Pirtobrutinib for treating relapsed or refractory chronic lymphocytic leukaemia after a BTK inhibitor [ID6269]

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

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

The evaluation 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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using pirtobrutinib in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 11 May 2026
- Details of the evaluation committee are given in section 5

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1 Recommendations

1.1 Pirtobrutinib can be used as an option to treat relapsed or refractory chronic lymphocytic leukaemia (CLL) in adults who have had a Bruton's tyrosine kinase (BTK) inhibitor, only if:

- retreatment with a covalent BTK inhibitor (including after fixed-duration regimens) is not clinically appropriate
- the company provides it according to the commercial arrangement (see section 2).

1.2 This recommendation is not intended to affect treatment with pirtobrutinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

What this means in practice

Pirtobrutinib must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option. Pirtobrutinib must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that pirtobrutinib provides benefits and value for money, so it can be used routinely across the NHS in this population.

Why the committee made these recommendations

Standard treatment for relapsed or refractory CLL in adults after a BTK inhibitor is venetoclax alone or venetoclax plus rituximab. Some people may have another covalent BTK inhibitor if they stopped using the first covalent BTK inhibitor either

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because they completed the fixed course of treatment or because of its side effects. Standard treatment for people who have tried a venetoclax regimen and a covalent BTK inhibitor is idelalisib plus rituximab.

Clinical trial evidence shows that people having pirtobrutinib have longer before their condition gets worse than people having either idelalisib plus rituximab or bendamustine plus rituximab (which is no longer widely used in the NHS). The evidence also suggests that people having pirtobrutinib may live longer than people having these treatments, but this is uncertain. Indirect comparisons suggest that people having pirtobrutinib may have a similar amount of time before their condition gets worse as people having venetoclax alone or venetoclax plus rituximab. There is limited evidence comparing pirtobrutinib with covalent BTK inhibitors in people with CLL that has been previously treated.

When comparing pirtobrutinib with idelalisib plus rituximab, the most likely cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources.

Assumptions of clinical similarity support cost comparisons against venetoclax alone and venetoclax plus rituximab. These suggest that costs for pirtobrutinib are similar to or lower than costs for venetoclax alone or venetoclax plus rituximab. But there is not enough evidence to support a cost-effectiveness comparison against covalent BTK inhibitors.

So, pirtobrutinib can be used only if retreatment with a covalent BTK inhibitor (including after fixed-duration regimens) is not clinically appropriate.

2 Information about pirtobrutinib

Marketing authorisation indication

2.1 Pirtobrutinib (Jaypirca, Eli Lilly & Company) is indicated for ‘the treatment of adults with relapsed or refractory chronic lymphocytic leukaemia (CLL) who have been previously treated with a BTK inhibitor’.

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Dosage in the marketing authorisation

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

Price

2.3 The list price for pirtobrutinib is £2,081.50 for a 28-pack of 50-mg tablets and £8,326.00 for a 56-pack of 100-mg tablets (excluding VAT; from company submission).

2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes pirtobrutinib available to the NHS with a discount. The size of the discount is commercial in confidence.

Sustainability

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Eli Lilly & Company will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by Eli Lilly & Company, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 Chronic lymphocytic leukaemia (CLL) is a malignant disorder of white blood cells and is the most common type of leukaemia in England. CLL usually progresses slowly. Symptoms develop gradually over time. The symptoms and frequent infections can have a big impact on daily life and overall wellbeing for people with CLL. A diagnosis of CLL can have a psychological impact on people with the condition and their families. The patient experts highlighted that the ‘watch and wait’ period often brings

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uncertainty and anxiety. People worry about disease progression, treatment failure and mortality. The patient experts explained that living with CLL is a constant cycle between watch and wait, increasing burden of symptoms, treatment, periods of good health, and relapse. Younger people with CLL may feel more stress because they may have many of these cycles ahead of them and because of work and family responsibilities. Older people with CLL may isolate themselves to avoid infections, which can lead to loneliness and depression. The patient experts explained that CLL has serious physical effects and causes emotional strain for people with CLL and their families, which can make everyday life very difficult. They also emphasised that some people can remain on the same treatment for many years, while others relapse after a short time, so a wide variety of treatment options is needed. Small lymphocytic lymphoma (SLL) is a different form of the same disease. CLL is present in the bone marrow and blood, whereas SLL is present mainly in the lymph nodes. The company stated that CLL and SLL are used interchangeably and thought this evaluation would apply to both. The committee noted that pirtobrutinib's marketing authorisation was specific to CLL but that in BRUIN-CLL-321, the main clinical trial for pirtobrutinib, about 8% of people had SLL and the rest had CLL. It requested further clinical input to clarify whether SLL and CLL were the same condition and whether the marketing authorisation for pirtobrutinib would also cover SLL.

Clinical management

Treatment options and positioning

3.2 There are various drug classes available to treat CLL and these are sometimes used in different combinations. These classes include:

- BCL2 inhibitors (BCL2is), such as venetoclax

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- covalent Bruton's tyrosine kinase inhibitors (cBTKis), such as acalabrutinib, ibrutinib or zanubrutinib
- anti-CD20 antibodies, such as rituximab or obinutuzumab
- PI3K delta inhibitors, such as idelalisib.

First-line treatments for CLL include venetoclax plus ibrutinib (VenI), venetoclax plus obinutuzumab, or acalabrutinib, ibrutinib or zanubrutinib monotherapy. Treatment choice is dependent on several factors, including patient fitness, the presence of specific genetic mutations, other clinical factors and individual preference. Later lines of treatment also depend on responses to previous lines and may consider treatment rechallenge in some cases, or trialling new drug classes in others. There is a range of NICE-recommended treatment options for relapsed or refractory CLL, including, but not limited to, idelalisib plus rituximab (IdelaR), venetoclax plus rituximab (VenR), venetoclax monotherapy (Ven-mono), and acalabrutinib, ibrutinib or zanubrutinib monotherapy. So, each person's treatment is individualised, depending on what treatment decision was appropriate at the time of treatment choice. The committee noted that, in some cases, people with CLL can have many lines of treatment throughout the treatment pathway. It also noted that there have been recent changes to the treatment pathway. This means that some chemoimmunotherapy options are no longer routinely used in clinical practice, such as fludarabine plus cyclophosphamide and rituximab and bendamustine plus rituximab (BR). In NICE's technology appraisal guidance on ibrutinib with venetoclax for untreated CLL, clinical experts and the NHS England representative noted that fludarabine plus cyclophosphamide and rituximab is occasionally used by smaller centres that lack access to alternative treatment options. They also confirmed that bendamustine plus rituximab is now rarely used in clinical practice in England. Pirtobrutinib is a non-covalent BTK inhibitor

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(BTKi), which means it inhibits the same target as cBTKis but binds it in a different way. Pirtobrutinib is expected to be offered to people with relapsed or refractory CLL after a BTKi. Clinical experts noted that a non-covalent BTKi like pirtobrutinib is useful at this stage in the treatment pathway. One expert said pirtobrutinib is particularly helpful for older people or people with impaired kidney function who may not be eligible for venetoclax plus rituximab, which carries a risk of tumour lysis syndrome. Patient experts preferred the at-home, oral administration of pirtobrutinib, which limited the time people with the condition spend in hospitals for treatment. One expert noted some people have side effects, such as nausea and headaches, but these become less frequent over time. Clinical and patient experts agreed that pirtobrutinib is better tolerated for many people than existing treatments. The committee noted the heterogeneity of treatment pathways because of the various treatment options available. It also thought that the proposed positioning of pirtobrutinib is not clearly defined, because there are multiple treatment options and positions within the treatment pathway for people who have had a BTKi. So, it concluded that pirtobrutinib would be considered in multiple populations in the treatment pathway. It considered multiple treatments to be relevant comparators with pirtobrutinib for different populations in this evaluation (see section 3.8).

Comparators

VenR

3.3 VenR is recommended by NICE as an option for CLL for people who have had at least 1 previous treatment. So, it may be used after first-line treatment with a cBTKi or a previous venetoclax regimen (which may be in combination with a cBTKi). The committee noted this was within the licensed population for pirtobrutinib and a relevant comparator for this evaluation. The company highlighted that a British Society for

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Haematology guideline suggested that, if someone's CLL relapsed within 3 years of fixed-duration venetoclax treatment, then switching to a BTKi is generally preferred. Also that, for later relapse, rechallenge with venetoclax-based therapy was reasonable. Clinical experts highlighted that venetoclax-based rechallenge would be offered if there was relapse 2 to 3 years after initial treatment. The committee considered this context for the relevancy of VenR as a comparator in the treatment pathway.

Ven-mono

3.4 Ven-mono is recommended by NICE as an option for CLL with a TP53 mutation or a 17p deletion for people when a B-cell receptor pathway inhibitor is unsuitable, or whose disease has progressed after a B-cell receptor pathway inhibitor (see NICE's technology appraisal guidance on venetoclax for treating CLL). The company thought that Ven-mono was not standard care in the UK based on clinical expert consultation. So, it did not include Ven-mono as a relevant comparator to pirtobrutinib in its submission. Clinical advice to the EAG was that Ven-mono is rarely used in NHS practice because it is less effective than VenR, so the EAG agreed it was not a relevant comparator. But, clinical experts at the committee meeting disagreed with both the company and the EAG, saying that Ven-mono is used in clinical practice for relapsed or refractory CLL, particularly when rituximab may be unsuitable. A clinical expert explained that there was real-world evidence suggesting that Ven-mono has similar efficacy to VenR in this setting. The committee concluded that Ven-mono could be used at the same point in the treatment pathway as pirtobrutinib for its licensed population, and therefore was a relevant comparator for this evaluation. It noted that no clinical evidence had been presented for this population. It requested modelling of Ven-mono as a relevant comparator, with further commentary and discussion of the circumstances around the population that would have Ven-mono in clinical practice. It also noted that further understanding around Ven-mono may be helpful for

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considering the comparison with VenR, if there is sufficient evidence for an indirect comparison with pirtobrutinib.

Retreatment with cBTKis

3.5 cBTKis are recommended by NICE as an option for untreated CLL in:

- NICE's technology appraisal guidance on acalabrutinib for treating CLL
- NICE's technology appraisal guidance on ibrutinib for treating CLL
- NICE's technology appraisal guidance on zanubrutinib for treating CLL.

But cBTKIs can also be used after relapse. The company said it could not identify published literature or data to understand outcomes for cBTKi retreatment or its use in the NHS. The clinical experts explained that most people who have cBTKis for untreated CLL remain on this treatment until disease progression, with very few people stopping because of intolerance. After progression on a cBTKi, treatment with another cBTKi is not usually effective or offered. In the event of stopping a cBTKi because of intolerance, clinical experts explained that they may adopt a watch-and-wait approach then consider switching to a different cBTKi. So, the clinical experts did not think that cBTKis would be a relevant comparator for pirtobrutinib. This is because pirtobrutinib's licensed indication is for after a cBTKi treatment, and in clinical practice retreatment is not used after progression. But, the EAG highlighted that first-line treatment with VenI used a fixed duration of ibrutinib for a maximum of 15 cycles (12 of those with venetoclax), which would mean most people stop treatment at the end of the regimen instead of because of disease progression. It considered that retreatment with a cBTKi would be possible for this population. The EAG identified the CAPTIVATE trial. This was a multicentre phase 2 study evaluating whether treatment could be safely stopped based on very low levels of cancer cells (minimal residual disease) after people with CLL complete first-line fixed-duration VenI treatment. The

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CAPTIVATE trial showed that most people whose CLL relapsed after treatment with VenI still had a response to retreatment with ibrutinib, which supports retreatment with a cBTKi in this context. The committee recognised that fixed-duration VenI had only recently been recommended by NICE, meaning standard care for people whose CLL relapses after this treatment has not been fully established yet. The company agreed. It thought that cBTKi retreatment may only be offered to a smaller population. The committee also noted that other fixed-duration regimens that include a cBTKi may be available in the future, so understanding the role of retreatment with a cBTKi will continue to be important. It noted that the population eligible for a second cBTKi after VenI treatment may increase over time as more people's CLL relapsed after treatment with VenI. But this was uncertain because people whose disease relapsed after 3 years might have another venetoclax-containing regimen. The committee concluded that cBTKis would be a relevant comparator for people who:

- stopped a cBTKi because of intolerance and were therefore eligible for retreatment with a cBTKi, or
- have had fixed-duration regimens of cBTKI treatments as a first-line treatment.

IdelaR

3.6 IdelaR is recommended by NICE as an option for CLL that has relapsed within 24 months of treatment (see NICE's technology appraisal guidance on idelalisib for treating CLL). NICE's technology appraisal guidance on zanubrutinib for treating CLL noted that IdelaR is rarely used in clinical practice because of its intensive dosing regimen and associated increased risk of infection. A clinical written submission and the EAG's clinical expert advised that IdelaR is not widely used because of its toxicity. The clinical experts highlighted that, although it is not widely used, IdelaR remains an important treatment option when other options are

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exhausted. They also noted that, although the population with relapsed or refractory CLL is small, the number of people having IdelaR is considered meaningful. The committee agreed that although use of IdelaR is limited, it may be an important comparator at later lines when other options are exhausted. But, it noted that the positioning of IdelaR is likely to be later in the treatment pathway than the other comparators, and noted the limitations of the clinical evidence compared against IdelaR (see section 3.14). It concluded that IdelaR was a relevant comparator for a small proportion of the eligible population.

Best supportive care

3.7 Best supportive care represents treatments for infections or supportive treatments for symptom control, such as blood products. The aim of best supportive care is to relieve symptoms of CLL and improve health-related quality of life. The clinical experts explained that in most cases they would offer an active treatment (such as retreatment with previous treatments or IdelaR) if available or enrol the patient in a clinical trial. Best supportive care would only be used for CLL in people with frailty and when the CLL is unlikely to respond to treatment options. The committee concluded that best supportive care is not a relevant comparator for this evaluation because it would probably be used in a later setting than pirtobrutinib.

Populations in the evaluation

3.8 Based on the entire discussion around comparators and the clinical treatment pathway (see sections 3.3 to 3.7), the committee thought it was most appropriate to consider 3 identified relevant populations that are within pirtobrutinib's marketing authorisation. For these populations, dual exposed means that they have had both a cBTKi and a BCL2i, either in sequence or in combination. These populations are:

- Population 1: 'Post-cBTKi or dual-exposed population for whom venetoclax is suitable'. This population may have had prior treatment

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with fixed-duration VenI but their CLL progressed 2 to 3 years or more after finishing treatment. They may also have had prior treatment with venetoclax plus obinutuzumab at first line and then a cBTKi treatment afterwards. The comparator for this population is likely to be VenR or Ven-mono.

- Population 2: 'Post-cBTKi or dual-exposed population for whom cBTKis are suitable'. This population may have had prior treatment with fixed-duration VenI but retreatment with a venetoclax-containing regimen is not suitable (either because of intolerance or because their CLL progressed on treatment or within 2 to 3 years of finishing treatment). People may also have had prior treatment with a cBTKi but stopped because of intolerance. The comparator for this population is likely to be cBTKis.
- Population 3: 'Post-cBTKi or dual-exposed population for whom BCL2is or cBTKis are not suitable'. This population may have had prior treatment with VenI but their CLL is refractory to both cBTKis and BCL2is. The comparator for this population is IdelaR and the pivotal trial evidence is directly relevant to this comparison.

The committee thought that population 1 was the most likely population to have pirtobrutinib in clinical practice and population 2 was relevant with potential to increase in size. But it recognised that the strongest comparative clinical evidence was for population 3 (see sections 3.9 to 3.11).

Clinical effectiveness

Data sources

3.9 The company presented evidence for pirtobrutinib from the BRUIN CLL-321 trial. This is an ongoing phase 3, open-label, randomised, multicentre trial in people with a confirmed diagnosis of relapsed or refractory CLL previously treated with a cBTKi. Participants were randomised in a 1 to 1

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ratio to pirtobrutinib (n=119) or investigator's choice (IdelaR [n=82] or BR [n=37]). The primary outcome was progression-free survival (PFS) assessed by an independent review committee (IRC). Key secondary outcomes included overall survival (OS), duration of response, time to next treatment, event-free survival, and measures of symptoms, physical function and safety. Pirtobrutinib improved IRC-assessed PFS compared with investigator's choice, with a hazard ratio (HR) of 0.536 (95% confidence interval [CI] 0.347 to 0.829) in people with prior venetoclax treatment and 0.621 (95% CI 0.385 to 1.001) in people without prior venetoclax treatment. In BRUIN CLL-321, 75.8% (50 of 66) of eligible people in the investigator's choice arm crossed over to pirtobrutinib after IRC-confirmed disease progression. The company adjusted for treatment switching in OS analyses using methods such as a rank-preserving structural failure time model (RPSFTM), inverse probability censoring weighting (IPCW) and a 2-stage accelerated failure time (AFT) approach. The EAG noted uncertainty in the intention-to-treat unadjusted OS results, with a HR of 1.090, a wide 95% CI (0.679 to 1.749) and overlapping Kaplan–Meier curves. Pirtobrutinib numerically improved OS compared with investigator's choice when adjusted for treatment switching using the 2-stage AFT method. The EAG thought the 2-stage AFT method was the most appropriate approach for adjusting for treatment switching. This is because it is more robust than IPCW when switching rates are high and it avoids reweighting non-switchers, so there is less bias. The HR for OS for pirtobrutinib compared with investigator's choice using the AFT method was 0.776 (95% CI 0.479 to 1.258).

BRUIN CLL-321 was used as the main clinical evidence source in the cost–utility model (see section 3.14). The committee concluded that pirtobrutinib increases both PFS and OS compared with investigator's choice, when adjusting for treatment crossover. But the committee noted that a key limitation of the clinical evidence was that it only compared

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pirtobrutinib against a comparator of investigator's choice which contained a treatment that is used last line in NHS clinical practice and a treatment that is not used in NHS clinical practice (see section 3.14).

Indirect treatment comparisons and other evidence

3.10 The company did a systematic review and feasibility assessment for indirect treatment comparisons (ITCs) for pirtobrutinib with other identified comparators in people who had previous treatment with a cBTKi, referred to from here as the scoped population. It thought there was substantial heterogeneity in treatment effect modifiers and prognostic markers across the included studies that made ITCs infeasible. Also, most of the identified trials did not include people who had previously had a cBTKi. The company claimed that ITCs would be unreliable because they would favour treatments for less aggressive CLL. The EAG agreed that ITCs in the scoped population were not appropriate for comparing pirtobrutinib and the relevant comparators. But, it was very concerned about the lack of supporting evidence for relative efficacy of pirtobrutinib with the identified comparators. The company identified Al-Sawaf et al. (2024), an unanchored matching-adjusted indirect comparison (MAIC) comparing pirtobrutinib from BRUIN CLL-321 with Ven-mono from a phase 2 study (Jones et al. 2018) in a post-cBTKi population. The study reported hazard ratios for pirtobrutinib relative to Ven-mono of 1.01 (95% CI 0.58 to 1.73) for PFS and 0.64 (95% CI 0.25 to 1.67) for OS. This suggests that pirtobrutinib may have similar efficacy to Ven-mono. The company used the results of the MAIC to support an assumption of clinical equivalence between pirtobrutinib and Ven-mono. It also used this, based on a further assumption that Ven-mono was clinically equivalent to VenR, to support the assumption that pirtobrutinib was similar to VenR. The company did not provide comparative evidence against cBTKis in population 2. It said there was a lack of evidence and it thought that rechallenge with cBTKis was rare in NHS practice. The EAG welcomed the Al-Sawaf et al. study to

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inform comparisons with venetoclax comparators. But it noted that the hazard ratios had wide CIs, so equivalent efficacy had not been conclusively demonstrated. The committee acknowledged the paucity of available evidence and the limitations of ITCs in the scoped population. But, it needed more information to compare pirtobrutinib against the relevant identified comparators to be able to make recommendations. So, it requested further work to characterise the relative effect of pirtobrutinib against all relevant comparators, even if this needed assumptions of relative effect transportability from other populations, such as those with untreated CLL. It noted that the results from BRUIN CLL-314, which compares pirtobrutinib with ibrutinib in untreated or relapsed or refractory but cBTKi-naive CLL, may soon be available. It also recalled that there may be additional evidence that can further characterise the relative effects of Ven-mono and VenR, described by the clinical expert, which could form part of an evidence network. Although this would probably be very weak evidence, it could be informative for decision making to at least establish plausibility of clinical equivalence for a VenR cost comparison (see section 3.17).

Updated indirect treatment comparisons

3.11 After the first committee meeting, the company did a network meta-analysis (NMA) using reported PFS outcomes from BRUIN CLL-314, MURANO and 4 other trials in cBTKi-naive CLL. It used the results of this NMA to support the assumption of equivalence between pirtobrutinib and VenR after previous treatment with a BTKi. The results are considered confidential by the company and cannot be reported here. Both the company and the EAG agreed that the data from BRUIN CLL-314 was too immature to inform an ITC of OS. The EAG considered the populations of the trials in the NMA to be broadly aligned. But, it questioned whether results in cBTKi-naive CLL would be generalisable to a post-cBTKi population because previous treatment with a BTKi is a treatment effect

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modifier. It noted that the company also agreed this was a treatment effect modifier when it did the feasibility assessment. Also, it noted that the NMA assumes equivalence between IdelaR and BR, and this introduces uncertainty. The EAG was concerned that the CIs around the PFS hazard ratio were wide and included both clinically important benefit and clinically important harm. The company explored the observational study that the committee mentioned to see whether it showed any evidence that Ven-mono was equivalent to VenR, and therefore could be used indirectly to support the case for equivalence between VenR and pirtobrutinib. Mato et al. (2019) compared the efficacy of Ven-mono with that of VENcombo (venetoclax plus obinutuzumab [VenO] or VenR) in a heavily pretreated, high-risk CLL cohort. The study reported hazard ratios for Ven-mono relative to VENcombo of 1.0 (95% CI 0.6 to 1.8) for PFS and 1.2 (95% CI 0.6 to 2.3) for OS. This suggests that VenR, as part of VENcombo, may have similar efficacy to Ven-mono. The company thought this study generally supported equivalence between Ven-mono and VenR, but it was not appropriate because the comparator was pooled VenO and VenR, whereas VenO is typically used for untreated CLL. The EAG agreed that the study was not appropriate to support an assumption of clinical equivalence between Ven-mono and VenR because of the pooled comparator arm, the small number of people having VenR, and the wide CIs for PFS and OS that included clinically important benefit as well as clinically important harm. In the absence of alternative evidence, the company said that the unanchored MAIC and the NMA in untreated CLL sufficiently demonstrated equivalent efficacy between pirtobrutinib and both Ven-mono (see section 3.18) and VenR. The company noted the lack of evidence to compare pirtobrutinib with cBTKi retreatment (see section 3.5). The committee noted the results of the BRUIN CLL-314 trial, which reported a PFS hazard ratio of 0.73 (95% CI 0.47 to 1.13) for pirtobrutinib compared with ibrutinib in the cBTKi-naive relapsed or refractory population. It also noted the results of Eyre et al. (2026), which

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did a Bayesian NMA of 10 randomised controlled trials in untreated CLL. The NMA connected 2 treatment networks to compare pirtobrutinib against all cBTKi monotherapies. The analysis relied on an assumption that BR and a treatment arm containing either fludarabine plus cyclophosphamide and rituximab (FCR) or BR were equivalent. The results of the NMA showed that pirtobrutinib had:

- numerically higher, but not statistically significantly longer, PFS than both acalabrutinib and zanubrutinib
- statistically significantly longer PFS than ibrutinib
- statistically significantly longer PFS than venetoclax plus obinutuzumab.

Suitability of clinical evidence

3.12 The committee noted that the NMA suggested that pirtobrutinib may be numerically superior to venetoclax–obinutuzumab and that obinutuzumab was the same class of drug as rituximab. It also noted the results against the cBTKis. It thought that although broadly supportive of clinical equivalence between pirtobrutinib and the comparators, the results of the Eyre et al. NMA were associated with considerable uncertainty. A major source of uncertainty was that the evidence came from a cBTKi-naive population, and that previous cBTKi treatment was expected to be a treatment effect modifier. The committee recalled that cBTKi rechallenge following relapse on fixed-duration regimens may become more common over time (see section 3.5). But, it noted that many of these people would have stopped treatment after finishing the fixed-duration treatment, rather than progressing on the treatment, so it was plausible that previous cBTKi treatment might be less of an effect modifier for these people. It recalled the EAG's comments on the results of the CAPTIVATE trial (see section 3.5) and thought that this supported the idea that prior BTKi use might not have as large an effect in the post-VenI population as in a population whose CLL had progressed on a cBTKi. The committee recognised the

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importance of the implied sequencing of treatments to the positioning of pirtobrutinib. It was particularly disappointed by the lack of evidence comparing pirtobrutinib with cBTKis in the scoped population because pirtobrutinib also acts through BTK inhibition. It thought that assumptions within the clinical evidence networks and for transportability of a similar clinical effectiveness between treatment lines contributed to uncertainty. The committee concluded that, on balance, it was plausible to assume equivalence of clinical efficacy between pirtobrutinib and VenR and Ven-mono. However, it thought that there was not sufficient evidence to justify an assumption of equivalent clinically efficacy between pirtobrutinib and cBTKis, which may be of particular importance for sequencing within clinical decision-making.

Economic model

Company's modelling approach

3.13 The company presented a cost–utility analysis for the comparison of pirtobrutinib with IdelaR. The economic model was a partitioned survival model with 3 health states: progression free, progressed disease and death. It had a lifetime horizon (76 years in the model), although fewer than 1% of patients were alive in either treatment arm after 20 years. A 28-day cycle length was applied, consistent with the BRUIN CLL321 dosing schedule. On-treatment and off-treatment health states reflected the maximum duration of treatment. The model simulated 2 populations. The first was the post-cBTKi population. This included people with relapsed or refractory CLL who had previously had a cBTKi. The second was the dual-exposed population. This included people with relapsed or refractory CLL who had previously had both a cBTKi and a BCL2i, either in sequence or in combination. The committee concluded that the model structure was acceptable for decision making.

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Comparison of pirtobrutinib with IdelaR (population 3)

3.14 The company presented a cost–utility analysis comparing pirtobrutinib with IdelaR for people with relapsed or refractory CLL who previously had 1 or more cBTKis (population 3). Efficacy data was based on the investigator's choice of IdelaR or BR from BRUIN CLL-321. In the comparator arm of BRUIN CLL-321, 70.6% had IdelaR. The clinical experts said that BR is a chemoimmunotherapy and is rarely used in NHS practice for treating relapsed or refractory CLL. The EAG highlighted that IdelaR is slightly more effective than BR, so using data from the investigator's choice arm as a proxy for IdelaR may overestimate pirtobrutinib's relative efficacy. The committee thought that including BR in the data informing the IdelaR arm of the model might bias the model towards pirtobrutinib, and that this was associated with uncertainty. It concluded that this analysis was adequate for comparing pirtobrutinib with IdelaR in population 3.

Post-progression utility values

3.15 The company had limited utility data for the progressed-disease state from trial participants. It identified a utility value of 0.600, which it stated was from Holzner et al. (2004). The company used this value in its cost–utility model (see section 3.13). The EAG felt that this value was too low, noting it was lower than the baseline utility value in BRUIN CLL-321 (this value is considered confidential by the company and cannot be reported here). The EAG noted that the baseline utility in BRUIN CLL-321 represented people who were in a progressed-disease state (because people in the trial had already had previous treatments). It also explained that baseline utilities were based on the full trial population (who had an average of 3 lines of treatment) and it was assumed that the dual-exposed population had received more lines of treatment than the intention-to-treat population. The EAG thought that this suggested that there is little difference in progressed utility by line of treatment and it would be more accurate to

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model a single utility to reflect being in the progressed-disease state, regardless of the line of treatment. The committee noted that the progressed-disease utility was not a major driver of the estimates of cost effectiveness. The committee noted that it could not locate the utility value of 0.600 in Holzner et al. and it was unclear how it was derived from the cited paper, and therefore how relevant it was. So, the committee concluded that the 0.600 value was not appropriate to use without further explanation of the exact source of the value. It thought that the EAG's approach had more face validity and concluded that it would use the baseline utility from BRUIN CLL-321 for progressed disease in its decision making.

Costs of stem cell transplant

3.16 The company reported a total cost of £114,141 for allogeneic stem cell transplantation. For stem-cell harvesting, it used the number of submissions as weights from the NHS England 2023 to 2024 National Cost Collection, resulting in a weighted base-case cost of £5,992. The reported cost for allogeneic stem cell transplantation was £61,328, which included items SA20, SA21, SA27 and SA38. However, this approach did not fully align with the methodology used in NICE's technology appraisal guidance on tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 25 years and under. The EAG revised the cost estimates of allogeneic stem cell transplantation. The total cost was calculated as £48,153. For stem-cell harvesting, the weighting method was corrected by using finished consultant episodes rather than submissions. This resulted in a recalculated cost of £1,495, which is substantially lower than the company's estimate. For the allogeneic stem cell transplantation procedure, all relevant items from TA975 (SA20 to SA23, SA38, SA39) were included. This led to a revised weighted cost of £48,153, which is also lower than the company's estimate. These revisions only affect the cost–utility analysis. The

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company explained that the difference in each approach is because of variation in methodological choice. The committee felt that the EAG's approach for calculating stem cell transplant cost was more appropriate. It concluded that the EAG's approach was preferred, which involved using the number of finished consultant episodes to calculate the cost of stem-cell harvesting and including all relevant items associated with allogeneic stem cell transplantation.

Cost comparison with VenR (population 1)

3.17 The company submitted a cost-comparison analysis for a comparison of pirtobrutinib with VenR in post-cBTKi, BCL2i-naive and dual-exposed populations, because there was limited clinical evidence available (see section 3.10). The company adapted the cost–utility model but assumed that PFS, OS and time to treatment discontinuation for VenR were equal to those for pirtobrutinib. This assumption was based on results from the Al-Sawaf et al. MAIC (see section 3.10). In the absence of time on treatment data for VenR, both the company and the EAG modelled time on treatment as being the same for pirtobrutinib as for VenR. This was capped at 26 cycles for the analysis, in line with the fixed duration of VenR in clinical practice. The clinical experts explained that VenR and pirtobrutinib do not have the same biological mechanism or treatment dynamics, so there may be differences in how long people are treated for (that is, discontinuation and costs of treatment). The committee recalled its conclusion on equivalence of clinical efficacy between pirtobrutinib and VenR in the absence of other evidence. For consideration of time on treatment, the committee noted that the economic model was based on evidence from the BRUIN CLL-321 trial, which may be a more heavily pretreated population than population 1 in this appraisal. However, considering the time on treatment was fixed to be the same in both arms, the analysis represented a proportionate cost of treatment over approximately 2 years. The committee thought that although the modelling

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of time on treatment was uncertain, it was appropriate in the absence of other evidence. It concluded that the cost-comparison analysis was appropriate for decision-making for this comparison, despite differences in the biological mechanism and treatment dynamics.

Cost comparison with Ven-mono (population 1)

3.18 At the first committee meeting, the clinical experts explained that Ven-mono was a relevant comparator and was used in practice when rituximab may be considered unsuitable (see section 3.4). Having used the Al-Sawaf et al. unanchored MAIC to support a cost comparison of pirtobrutinib with VenR, the company provided a new cost-comparison analysis with Ven-mono. This used the same cost-comparison model as for VenR, with specific treatment and administration costs for pirtobrutinib and Ven-mono. The committee noted the uncertainty of the results from the unanchored MAIC. It concluded that a cost comparison was a reasonable approach for the comparison of VenR (see section 3.17) with Ven-mono in population 1 and that the company's and the EAG's base-case cost-comparison models were acceptable for decision making.

Cost comparison with a cBTKi (population 2)

3.19 The company did not provide any cost-effectiveness analyses comparing pirtobrutinib with cBTKis in post-cBTKi, BCL2i-naive, or dual-exposed populations because it did not think them an appropriate comparator (see section 3.5). At the first committee meeting, the EAG expressed strong concern about the lack of supporting evidence for pirtobrutinib compared with cBTKis. In the absence of evidence and as a last-resort approach, the EAG provided an exploratory cost-comparison analysis assuming equal efficacy. It provided cost comparisons of pirtobrutinib against acalabrutinib, ibrutinib and zanubrutinib in the post-cBTKi population. These analyses used the company's cost-comparison model for pirtobrutinib against VenR as a base. Adverse events were equal across

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treatments, and costs and dosing were adjusted for each cBTKi. The EAG thought it might be reasonable to assume similar efficacy against cBTKis for relapsed or refractory CLL, as with VenR. It thought that the available evidence suggests that cBTKis are at least as effective as BCL2is for first-line CLL. So, assuming similar efficacy for pirtobrutinib and VenR implies that assuming similar efficacy for pirtobrutinib against cBTKis for relapsed or refractory CLL may be reasonable. The committee acknowledged the EAG's cost comparison with cBTKis, noting that the importance of cBTKis as a comparator was uncertain. The committee recalled its concerns with the lack of evidence for equivalence of efficacy of pirtobrutinib compared to cBTKis (see section 3.12). It also noted the company had not presented this comparison and exploratory nature of the analysis conducted by the EAG. It concluded that it had not seen enough evidence to justify a cost-comparison analysis to evaluate pirtobrutinib against retreatment with cBTKis in the scoped population.

Severity

3.20 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). In cost–utility analyses, the committee may apply a greater weight to QALYs (a severity modifier) if technologies are indicated for conditions with a high degree of severity. For the population 3 comparison of pirtobrutinib with IdelaR, the modelling results of the committee's preferred base case indicated that the criteria for a severity modifier of 1.2 was not met. So, the committee concluded that a severity modifier should not be applied for decision making.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.21 The incremental cost-effectiveness ratios (ICERs) for the comparison with IdelaR in population 3 cannot be presented because the comparators

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have confidential patient access scheme prices. The ICER from the committee's preferred base-case was within the range normally considered a cost-effective use of NHS resources.

Cost comparison estimates

3.22 For the comparisons with Ven-mono and VenR, the committee concluded that cost-comparison analyses were acceptable given the lack of other evidence. The committee concluded that pirtobrutinib was an effective use of NHS resources in the comparisons with Ven-mono and VenR.

Acceptable ICER

3.23 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £25,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted that the analysis was associated with uncertainty, specifically that the pivotal trial evidence was immature. So, the committee concluded that an acceptable ICER would be towards the upper end of the range NICE considers a cost-effective use of NHS resources (£25,000 to £35,000 per QALY gained).

Preferred assumptions

3.24 The preferred assumptions were to:

- compare pirtobrutinib against VenR, Ven-mono, cBTKi monotherapies and IdelaR, but not against best supportive care (see sections 3.3 to 3.7)
- source the post-progression utility values from the BRUIN CLL-321 trial baseline values (see section 3.15)

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- calculate the cost for stem-cell harvesting using finished consultant episodes and including all relevant items in the allogeneic stem cell transplantation cost (see section 3.16)
- adopt cost-comparison approaches for comparisons with VenR and Ven-mono and, in the absence of evidence, use common adverse-event rates for pirtobrutinib and comparators (see sections 3.17 to 3.18)
- not adopt a cost-comparison approach for the comparison with cBTKi monotherapies (see section 3.19)
- not apply a severity QALY weighting to the population 3 base case (see section 3.20).

Other factors

Equality

3.25 The company's submission did not include equality evidence for adults with relapsed or refractory CLL who have had a BTKi. The committee did not identify any equality issues.

Uncaptured benefits

3.26 The company noted that the impact on carer quality of life was not captured in the economic analysis, but it did not provide qualitative detail. It highlighted that pirtobrutinib may reduce monitoring costs compared with venetoclax-containing regimens. This is because pirtobrutinib's safety profile avoids intensive hospitalisation and monitoring related to tumour lysis syndrome. The company noted that it chose to be conservative by assuming equivalent adverse events in cost comparisons. This means that those benefits were not captured in comparisons where pirtobrutinib had a preferable safety profile to other treatments. The company also stated that patient preference for orally administered treatments was not captured in the economic analysis. The EAG considered it difficult to assess the magnitude of any benefit from pirtobrutinib on carer quality of

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life because of a lack of evidence. It noted that the company only considered VenR in the original submission and included adverse events in the cost-comparison analysis with pirtobrutinib. The EAG also highlighted that most comparator treatments (cBTKis, idelalisib and venetoclax) are oral treatments, and any utility benefit from oral administration would likely be reflected in EQ-5D data from BRUIN CLL-321. The committee considered whether there were any uncaptured benefits of pirtobrutinib. It did not identify additional benefits of pirtobrutinib not captured in the economic modelling. So, the committee concluded that all additional benefits of pirtobrutinib had already been taken into account.

Conclusion

Recommendation

3.27 The committee considered the clinical evidence for pirtobrutinib for treating relapsed or refractory CLL after a BTKi, including its potential to improve PFS compared with IdelaR. But it noted that pirtobrutinib had not been directly compared with VenR, Ven-mono or cBTKis in the scoped population. It noted that although there was uncertainty with the cost-comparison estimates for these comparators, pirtobrutinib is likely be cost-saving compared with VenR and Ven-mono treatments. Pirtobrutinib was not compared with cBTKIs. The cost-effectiveness estimates for pirtobrutinib compared with IdelaR were within the range that NICE normally considers an acceptable use of NHS resources. So, pirtobrutinib can be used to treat relapsed or refractory CLL in adults only if retreatment with a covalent BTKi (including after fixed-duration regimens) is not clinically appropriate.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information

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Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of 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 cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England 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 guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

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 healthcare professional responsible for their care thinks that pirtobrutinib

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is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation 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 being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

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

Chairs

Richard Nicholas and Paul Arundel

Vice chair, technology appraisal committee C, and Chair, highly specialised technology appraisal committee

NICE project team

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

Sammy Shaw and Madiha Adam

Technical leads

Samuel Slayen

Technical adviser

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Leena Issa

Project manager

Adam Brooke

Principal technical adviser

ISBN: [to be added at publication]

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