NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Ibrutinib for treating relapsed or refractory mantle cell lymphoma

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ibrutinib 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?

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 determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using ibrutinib 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: 19 October 2017

Second appraisal committee meeting: 2 November 2017

Details of membership of the appraisal committee are given in section 6.

1 Recommendations

1.1 Ibrutinib is not recommended, within its marketing authorisation, for treating relapsed or refractory mantle cell lymphoma in adults.

1.2 The committee would consider a proposal for inclusion in the Cancer Drugs Fund that:

- demonstrates a plausible potential for cost effectiveness either in the whole population or a subgroup of the population
- details how additional data will address the clinical uncertainties described in section 4
- states the likelihood that additional data will reduce uncertainty enough to support positive guidance in the future
- proposes the method for data collection (for example, from an ongoing randomised controlled trial)

- states when the results will be available
- if appropriate data collection is not ongoing, and therefore data collection would be started to address the key areas of uncertainty, summarises the protocol specifying:
  - methodology
  - governance (including information governance, patient consent, and ethical approval)
  - data analysis
  - who will have access to the data and how the results will be published
  - who is accountable for monitoring and validation
  - funding arrangements.

1.3 This guidance is not intended to affect the position of patients whose treatment with ibrutinib was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

Description of the technology	Ibrutinib (Imbruvica, Janssen) inhibits a protein called Bruton's tyrosine kinase, stopping B-cell (lymphocyte) proliferation and promoting cell death.
Marketing authorisation	Ibrutinib has a marketing authorisation in the UK for the treatment of adults 'with relapsed or refractory mantle cell lymphoma'.
Adverse reactions	The most common adverse reactions associated with ibrutinib include diarrhoea, musculoskeletal pain, upper respiratory tract infection, haemorrhage, bruising, rash, and nausea. For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended dose and schedule	Ibrutinib is taken orally (4×140-mg capsules) once daily, until the disease progresses or there is unacceptable toxicity.
Price	Ibrutinib is available at the list price of £4,599.00 for 90×140-mg capsules (£51.10 per capsule) and £6,132.00 for 120×140-mg capsules (£51.10 per capsule; excluding VAT, British national formulary [BNF] June 2016). The company has agreed a patient access scheme with the Department of Health that applies to all indications for ibrutinib. If ibrutinib had been recommended, this scheme would provide a simple discount to the list price of ibrutinib with the discount applied at the point of purchase or invoice. The level of the discount increased during the appraisal and is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee (section 6) considered evidence submitted by Janssen and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of ibrutinib, having considered evidence on the nature of relapsed or refractory mantle cell lymphoma and the value placed on the benefits of ibrutinib by people with the condition, those who represent

them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical effectiveness

Clinical management of relapsed or refractory mantle cell lymphoma

4.1 The committee heard from the clinical expert that the most common first-line options for treating mantle cell lymphoma are rituximab in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP), or rituximab in combination with bendamustine. These are followed by 2 years of rituximab maintenance treatment. The committee understood that there is no accepted standard of care for treating relapsed or refractory mantle cell lymphoma, and that a range of chemotherapy regimens are used. It heard from the clinical expert that these often contain rituximab, even though many people will have had rituximab as part of first-line and maintenance treatment. The clinical expert highlighted that as many as 22 different treatments are used in the UK for treating relapsed or refractory mantle cell lymphoma. The choice of treatment largely depends on the availability of drugs and clinician's choice, because there is no treatment regimen that has been shown to be the most effective in this setting. The clinical expert also commented that temsirolimus, the comparator in the main ibrutinib study (RAY), is not used in the UK because it is considered to be of low efficacy despite being licensed for this indication. The committee concluded that there is no standard of care for treating relapsed or refractory mantle cell lymphoma in England, and that treatment tends to combine rituximab with a range of chemotherapy options. It also concluded that temsirolimus is not relevant to UK clinical practice.

Clinical need of patients with mantle cell lymphoma

4.2 The committee noted that mantle cell lymphoma is an aggressive form of non-Hodgkin's lymphoma and in some cases can be associated with debilitating symptoms. There are very high rates of relapse after initial

treatment, and a huge effect on quality of life. The committee heard from the patient and clinical experts that ibrutinib is already widely used in clinical practice because of its availability through the Cancer Drugs Fund, and is welcomed by patients because it is highly effective compared with existing treatments and extremely well tolerated with very few adverse reactions. It is taken orally and people value this highly because it can be taken in the privacy of their own home and reduces the need for hospital visits. It can be used by older and frail people and, unlike current chemotherapy options, patients do not usually need additional treatments to counter adverse reactions. For these reasons, the patient experts considered that ibrutinib is a life-transforming drug that results in a step change in the quality of life of patients with relapsed or refractory mantle cell lymphoma and their families and carers, allowing many to participate in general day-to-day activities, and very quickly return to their normal life. The committee concluded that the availability of an effective oral therapy with a manageable adverse-reaction profile is highly valued by patients and addresses a high unmet need among people with relapsed or refractory mantle cell lymphoma.

Overview of ibrutinib studies

4.3 The committee noted that the evidence on the clinical effectiveness of ibrutinib came from 1 randomised controlled trial (RAY) and 2 single-arm studies (SPARK and PCYC-1104). It considered that RAY is not strictly relevant to NHS practice because temsirolimus, the comparator treatment in the trial, is not routinely used in the UK. It noted the absence of any trials comparing ibrutinib with any comparator defined in the NICE scope. It also noted that all 3 studies were open-label, which made them potentially prone to bias, although it accepted that the studies addressed potential measurement bias by using an independent review committee to evaluate the primary outcome. The committee concluded that the studies were of a reasonable quality but were limited by the lack of a comparison against a treatment used in UK clinical practice.

Clinical evidence – trial results

4.4 The committee noted that at median follow up of 20 months, median progression-free survival in RAY was statistically significantly longer for ibrutinib compared with temsirolimus (14.6 months compared with 6.2 months; hazard ratio [HR] 0.43; 95% confidence interval [CI] 0.32 to 0.58; p<0.0001). It also noted that the overall-survival data from RAY are immature and that median overall survival had not yet been reached in the ibrutinib arm, indicating that more than 50% of patients were still alive. The committee understood that this represented a 24% reduction in the risk of death compared with temsirolimus but that this was not statistically significant (HR 0.76; 95% CI 0.53 to 1.09; p=0.1324). The committee explored the relationship between progression-free survival and overall survival. It heard from the clinical expert that progression-free survival is a reasonable surrogate for overall survival in this condition. However, the committee noted that this was unproven in the trial. The committee also noted that the crossover of 23% of patients in the temsirolimus arm to the ibrutinib arm could confound the estimate of overall survival for temsirolimus. The overall-survival results were also potentially confounded by the use of subsequent anticancer systemic therapies in both arms (31.7% of patients in the ibrutinib arm and 58.2% of patients in the temsirolimus arm). The committee concluded that the results from RAY suggest that ibrutinib significantly improves progression-free survival compared with temsirolimus but that the overall-survival benefits are uncertain. The committee noted with interest that the final overall-survival results from RAY are expected in 2017. It concluded that although these would be more mature they would still be potentially confounded by crossover and the use of further anticancer therapies, and so may not provide more robust data.

4.5 The committee considered that the results from the 2 single-arm trials were generally supportive of the results from RAY, although it noted that the overall-response rates and progression-free survival were slightly

lower in the single-arm trials than in the ibrutinib arm of RAY. It concluded that it was appropriate to pool the results from the 3 studies to give a larger patient population, given the general lack of evidence for treating relapsed or refractory mantle cell lymphoma with ibrutinib.

Indirect comparison

4.6 The committee noted that in the absence of any direct trial evidence for ibrutinib against a comparator reflective of current UK clinical practice, the company did an indirect treatment comparison using results from RAY and from the OPTIMAL study (Hess, 2009) that compared temsirolimus with clinician's choice of single-agent chemotherapy. The indirect treatment comparison compared ibrutinib against clinician's choice of single-agent chemotherapy in OPTIMAL, using temsirolimus as the common comparator. The committee noted that the company adjusted the treatment effect of chemotherapy, as estimated from the indirect comparison, to take into account the effect of adding rituximab (R-chemo). This adjustment used data on the benefit of R-chemo compared with single-agent chemotherapy from the Haematological Malignancy Research Network (HMRN) audit of 118 patients with mantle cell lymphoma that had been treated with first-line therapy. The committee understood that this resulted in a progression-free survival hazard ratio for ibrutinib compared with R-chemo of 0.28 (representing a 72% reduction in the risk of disease progression with ibrutinib compared with R-chemo).

4.7 The committee acknowledged the limitations of the indirect comparison that were highlighted by both the company and the evidence review group (ERG), such as differences in the patient populations in OPTIMAL and RAY. It also noted that the HMRN audit did not specifically relate to patients with relapsed or refractory mantle cell lymphoma. It also understood that the ERG did not agree with the company's 2-stage approach to estimating treatment effects for ibrutinib compared with R-chemo, and that the ERG had done a separate analysis based on a single-stage approach using a random effects network meta-analysis

instead of fixed effects. This resulted in a hazard ratio for progression-free survival of 0.27 (HR 0.27; 95% credible interval 0.06 to 1.26), similar to the company's estimate of 0.28. However, the committee noted that because of concerns about the evidence used to inform the indirect comparisons, the ERG considered that the results of both analyses should be interpreted with caution. The committee also noted that the company's alternative approach to estimating the effectiveness of ibrutinib compared with R-chemo (that is, assuming that temsirolimus has equal efficacy to R-chemo based on the results from RAY) produced a less-favourable hazard ratio of 0.43. The committee concluded that there is considerable uncertainty associated with the indirect comparisons and that the benefit of ibrutinib compared with R-chemo is unclear, although it accepted that the available evidence and experience from clinical practice strongly suggest that ibrutinib is more effective.

Subgroups

4.8 The committee discussed the efficacy results for subgroups of patients based on the number of previous lines of therapy taken by patients. It noted that the results from the studies suggested greater efficacy in patients who had ibrutinib after 1 prior therapy compared with 2 or more therapies. It also heard from the clinical expert that ibrutinib is particularly beneficial after the first relapse. However, the committee was concerned that the subgroups had been defined post hoc and it was therefore reluctant to draw any firm conclusions about the relative efficacy of ibrutinib in these groups.

Cost effectiveness

The company's model and the ERG's exploratory analyses

4.9 The committee noted that the company had developed a Markov model comparing ibrutinib with R-chemo, comprising 3 states (pre-progression, post-progression and death), and that this approach had been used in previous NICE appraisals. The committee was aware that overall-survival

data from the ibrutinib studies were not directly extrapolated but were modelled using progression-free-survival data from the pooled ibrutinib dataset. It recalled the clinical expert's view that progression-free survival is a reasonable proxy for overall survival and considered that, although this is unproven in the trial, the company's approach was not unreasonable given the immaturity of the overall-survival data.

4.10 The committee considered the ERG's critique of the company's model. It noted the ERG's comments that the company's Markov approach imposed structural constraints, which did not make the best use of the trial data on survival, and that the overall survival predicted by the model did not provide a good visual fit to the observed Kaplan–Meier survival curve from the trials. The committee understood that the ERG favoured a partitioned survival model using overall-survival data for ibrutinib directly from the trials rather than using progression-free survival, and had explored the effect of using this approach in an exploratory analysis (Set B). The committee examined the ERG's Set B exploratory analysis but was concerned that the partitioned survival approach resulted in efficacy estimates for R-chemo that were higher than those for ibrutinib, giving higher quality-adjusted life year (QALY) gains for R-chemo than ibrutinib. By contrast, it heard from the clinical expert that experience has shown that ibrutinib is more effective than R-chemo for treating relapsed or refractory mantle cell lymphoma. This is partly because relapsed or refractory disease will already have been treated with R-chemo and rituximab maintenance therapy, which will become progressively less effective with further relapse. The committee concluded that the results of the partitioned survival analysis are not clinically plausible, acknowledging the ERG's comments that they are associated with major uncertainty because they used the outputs of a highly uncertain meta-analysis.

4.11 The committee re-examined the company's Markov approach, which it considered led to more plausible results (incremental QALYs for ibrutinib compared with R-chemo ranging from 0.82 to 1.87 depending on the

scenario), although it acknowledged the considerable uncertainty associated with these estimates. The committee noted that in the company's base-case analysis, incorporating the updated patient access scheme, the incremental cost-effectiveness ratio (ICER) for ibrutinib compared with R-chemo was £62,650 per QALY gained. It also noted that the company carried out a range of scenario analyses to test the assumptions in the model. These included estimating the effectiveness of ibrutinib compared with R-chemo using temsirolimus as a proxy for R-chemo. The committee noted that this scenario used the efficacy data from RAY and resulted in an estimated ICER for ibrutinib compared with R-chemo of £69,142 per QALY gained. The committee was aware that in all but 1 of the scenarios presented by the company, the ICER was above £59,000 per QALY gained. In the remaining scenario the company applied a hazard ratio to post-progression survival for R-chemo, adjusting it to be as close as possible to the anticipated survival based on the results of the HMRN audit (that is, 8.4 months for patients on second-line treatment). This resulted in an ICER of £49,849 per QALY gained. However, the committee understood that time-to-event estimates for progression-free survival and post-progression survival for ibrutinib were taken from the 1 prior therapy subgroup only, and therefore that the analysis reflected this subgroup. The committee recalled its earlier conclusion that it was reluctant to draw any firm conclusions about the relative efficacy of ibrutinib in groups of patients based on the number of previous lines of therapy they have had (see section 4.8) and was reluctant to accept this ICER as suitable for decision-making. It also noted that the company had not suggested that it would be appropriate to only consider ibrutinib for a subgroup of patients who have had only 1 prior therapy.

4.12 The committee was aware that the ERG had made adjustments to some of the parameter values in the company's model in a set of exploratory analyses (Set A). In most instances, this resulted in a lower ICER for ibrutinib compared with R-chemo than that estimated by the company. However, the committee was minded not to accept the results of the

ERG's amendments because these represented the extreme (lowest) end of the ERG's wide estimate of possible ICERs, depending on the model and parameters used. The committee concluded that the company's model was in line with accepted NICE methods and was appropriate for decision-making. However, it considered that the ICERs presented by the company, incorporating the confidential patient access scheme for ibrutinib, were above the range normally considered a cost-effective use of NHS resources (that is, £20,000 to £30,000 per QALY gained) for the whole population of people with relapsed or refractory mantle cell lymphoma.

4.13 After consultation on the appraisal consultation document, the company submitted a later data-cut from the HMRN audit, which it considered supported the methods used to estimate the effectiveness of R-chemo in the cost-effectiveness analysis. The company stated that this additional data supported the assumption of equivalent efficacy of R-chemo regimens in relapsed or refractory disease, acknowledging that this was based on a small number of patients and had wide confidence intervals. The audit also showed very similar overall survival and progression-free survival for R-chemo to those calculated in the company's model. The company noted that their base-case model may have slightly overestimated the effect on progression-free survival of adding rituximab to chemotherapy and therefore overestimated the overall treatment effect of R-chemo. This would have lowered the progression-free survival hazard ratio for the comparison of ibrutinib with R-chemo from 0.28 (see section 4.6) to 0.24. However, if the lower hazard ratio for progression were implemented in the model this would have only a small effect on the ICER, reducing it by approximately £2,000. The committee agreed that this additional data provided some reassurance about the method of modelling the company had used, and reiterated that it considered the company's original model and base-case ICER to be acceptable for decision-making. However, the ICER calculated by the company was

higher than the committee could accept as a cost-effective use of NHS resources.

End-of-life considerations

4.14 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's final Cancer Drugs Fund technology appraisal process and methods. It accepted that ibrutinib is indicated for people with a short life expectancy, noting that the estimates presented for people with relapsed or refractory mantle cell lymphoma ranged from 5.2 months to 9.7 months. It also accepted that there is enough evidence to indicate that ibrutinib offers an extension to life of at least an additional 3 months, compared with current NHS treatment. The committee concluded that ibrutinib met all the criteria to be considered a life-extending end-of-life treatment.

4.15 Taking all the evidence and uncertainties together, and given the extra weight applied to QALYs at the end of life, the committee concluded that the ICERs estimated by the company remained above the range normally considered to be a cost-effective use of NHS resources.

Innovation

4.16 The committee discussed the innovative aspects of ibrutinib. It accepted that the treatment has several benefits for people including oral administration, manageable adverse reactions and low toxicity. The committee concluded that ibrutinib could be considered a step change in managing relapsed or refractory mantle cell lymphoma. However, it did not consider that any additional health-related benefits, that had not been captured fully in the QALY calculation, would be enough to lower the ICER to within the range normally considered cost effective. Therefore, the committee was unable to recommend ibrutinib for treating relapsed or refractory mantle cell lymphoma.

Cancer Drugs Fund

4.17 The committee was aware that ibrutinib had previously been available through the Cancer Drugs Fund, and considered whether it would be appropriate to recommend ibrutinib for inclusion in the new Cancer Drugs Fund. If an appraisal committee concludes that the uncertainty in the clinical and cost-effectiveness data is too great to recommend the drug for routine use, it can consider a recommendation for use within the Cancer Drugs Fund if the ICERs presented have the plausible potential for satisfying the criteria for routine use, and if it is possible that the clinical uncertainty can be addressed through collection of outcome data, normally within 2 years. The committee was aware that the company had initially requested that ibrutinib remain in the Cancer Drugs Fund in order to collect further evidence on areas of uncertainty including the overall survival benefit of ibrutinib, quality-of-life estimates, and effectiveness compared with R-chemo, but that it had subsequently asked NICE to consider ibrutinib for routine commissioning instead. The committee concluded that, at the current price agreed in the patient access scheme, the ICER was outside the range that could be considered cost effective for routine commissioning for the whole population of people with relapsed or refractory mantle cell lymphoma. However, in view of the uncertainties in the evidence including the overall survival benefit, it considered that it would be worthwhile to give the company the opportunity to make a case for continued inclusion in the Cancer Drugs Fund, either for the whole population or a subgroup of the population, outlining the evidence that would be collected over the next 2 years.

Potential equality issues

4.18 The committee noted the potential equality issue raised by the company and patient groups that ibrutinib would offer an alternative to less effective but better tolerated chemotherapy agents for older or frailer people. It also noted the issue raised that oral administration allows an effective treatment option for people without access or transport to an infusion unit

and significantly reduces multiple hospital visits. The committee acknowledged that access to ibrutinib may enhance treatment in these groups of people, but it was unable to recommend ibrutinib because it could not be considered a cost-effective use of NHS resources.

Pharmaceutical Price Regulation Scheme (PPRS) 2014

4.19 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Summary of appraisal committee's key conclusions

TAXXX	**Appraisal title: Ibrutinib for treating relapsed or refractory mantle cell lymphoma**	**Section**
Key conclusion		
Ibrutinib is not recommended, within its marketing authorisation, for treating relapsed or refractory mantle cell lymphoma in adults. The committee concluded that the company's model was in line with accepted NICE methods and was appropriate for decision-making. However, it considered that the incremental cost-effectiveness ratios (ICERs) presented by the company, incorporating the updated confidential patient access scheme for ibrutinib, were above the range normally considered a cost-effective use of NHS resources		1.1 4.12

(that is, £20,000 to £30,000 per quality-adjusted life year [QALY] gained) for the whole population of people with relapsed or refractory mantle cell lymphoma. The committee concluded that ibrutinib met all the criteria to be considered a life-extending end-of-life treatment but that, taking into account the extra weight applied to QALYs at the end of life, the ICERs remained above the range normally considered to be a cost-effective use of NHS resources. The committee concluded that the overall-survival benefit of ibrutinib is uncertain because of the immaturity of the data from the RAY study. It also concluded that there is considerable uncertainty associated with the indirect comparisons, and that the size of the benefit of ibrutinib compared with chemotherapy plus rituximab (R-chemo) is unclear. The committee would consider a proposal for inclusion in the Cancer Drugs Fund, either for the whole population or a subgroup of the population, outlining the evidence that would be collected over the next 2 years.		4.14, 4.15 4.4, 4.7 1.2, 4.17
Current practice		
Clinical need of patients, including the availability of alternative treatments	The committee concluded that the availability of an effective oral therapy with a manageable adverse-reaction profile is highly valued by people, and addresses a high unmet need for people with relapsed or refractory mantle cell lymphoma.	4.2
The technology		

Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee accepted that ibrutinib has several benefits for people including oral administration, manageable adverse reactions and low toxicity. The committee concluded that ibrutinib could be considered a step change in managing relapsed or refractory mantle cell lymphoma.	4.2, 4.16
What is the position of the treatment in the pathway of care for the condition?	Ibrutinib has a marketing authorisation in the UK for the treatment of adults 'with relapsed or refractory mantle cell lymphoma'.	2
Adverse reactions	The committee understood that ibrutinib is extremely well tolerated with very few adverse reactions.	4.2
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The committee understood that the clinical evidence for ibrutinib came from 1 randomised controlled trial (RAY), in which ibrutinib was compared with temsirolimus, and 2 single-arm studies (SPARK and PCYC-1104). The committee concluded that the studies were of a reasonable quality but were limited by the lack of a comparison against a treatment used in UK clinical practice.	4.3

Relevance to general clinical practice in the NHS	The committee considered that RAY was not strictly relevant to NHS practice because temsirolimus, the comparator treatment in the trial, is not routinely used in the UK.	4.3
Uncertainties generated by the evidence	The committee concluded that the overall-survival benefits from RAY were uncertain because of the immaturity of the data, the crossover of 23% of patients in the temsirolimus arm to the ibrutinib arm, and the use of further anticancer systemic therapies in both arms. The committee was aware that there is considerable uncertainty associated with the indirect comparisons and that the size of the benefit of ibrutinib compared with R-chemo is unclear.	4.4 4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The committee discussed efficacy results for subgroups of patients based on the number of previous lines of therapy taken. However, it was reluctant to draw any firm conclusions because of the post-hoc nature of the analyses.	4.8

Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee concluded that the results from RAY suggest that ibrutinib significantly improves progression-free survival compared with temsirolimus. The committee considered that the results from the 2 single-arm studies were generally supportive of the results from RAY. It concluded that it was appropriate to pool the results from the 3 studies to give a larger patient population, given the general lack of evidence for treating relapsed or refractory mantle cell lymphoma with ibrutinib.	4.4, 4.5
Evidence for cost effectiveness		
Availability and nature of evidence	The company developed a Markov model, comparing ibrutinib with R-chemo, with 3 states (pre-progression, post-progression and death). The committee was aware that overall-survival data from the ibrutinib studies were not directly extrapolated but were modelled using progression-free survival data from the pooled ibrutinib dataset. It concluded that the company's approach was not unreasonable given the immaturity of the overall-survival data.	4.9

Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee understood that the evidence review group (ERG) favoured a partitioned survival model using overall-survival data directly from the trials rather than using progression-free survival, and had explored the effect of using this approach. However, the committee concluded that the results of the partitioned survival analysis were not clinically plausible, acknowledging the ERG's comments that they were associated with major uncertainty because they used the outputs of a highly uncertain meta-analysis. The committee considered that the company's Markov approach led to more plausible results, although it acknowledged the considerable uncertainty associated with these estimates. The committee did not consider that the additional analyses submitted by the company after consultation reduced the ICER for ibrutinib compared to R-chemo to a level considered to be a cost-effective use of NHS resources.	4.10 4.11 4.13

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The committee did not consider that any additional health-related benefits that had not been captured fully in the QALY calculation would be enough to lower the ICER to within the range normally considered cost effective.	4.16
Are there specific groups of people for whom the technology is particularly cost effective?	The committee made no specific recommendations for any subgroups.	
What are the key drivers of cost effectiveness?	The committee was aware that in all but 1 of the scenarios presented by the company, the ICER was above £59,000 per QALY gained.	4.11

Most likely cost-effectiveness estimate (given as an ICER)	The committee concluded that the ICERs presented by the company, incorporating the updated confidential patient access scheme for ibrutinib, were above the range normally considered cost effective, taking into account the extra weight applied to QALYs at the end of life.	4.12, 4.15
Additional factors taken into account		
Patient access schemes (PPRS)	The company has agreed a patient access scheme with the Department of Health that applies to all indications for ibrutinib. The level of the discount increased during the appraisal and is commercial in confidence.	2, 4.11
End-of-life considerations	The committee concluded that ibrutinib met all the criteria to be considered a life-extending end-of-life treatment.	4.14
Equalities considerations and social value judgements	The committee acknowledged that access to ibrutinib may enhance treatment for older, frailer people by offering an alternative to less effective but better tolerated chemotherapy for these people. It also acknowledged that oral administration allows an effective treatment option for people without local access or transport to an infusion unit.	4.18

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.

Jane Adam
Chair, appraisal committee
December 2016

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 A.

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.

Sana Khan
Technical Lead

Zoe Charles
Technical Adviser

Marcia Miller and Liv Gualda

Project Managers

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