

# Ibrutinib for treating Waldenstrom's macroglobulinaemia

Technology appraisal guidance

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[www.nice.org.uk/guidance/ta491](http://www.nice.org.uk/guidance/ta491)

## Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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## 1 Recommendations

- 1.1 Ibrutinib is recommended for use in the Cancer Drugs Fund as an option for treating Waldenstrom's macroglobulinaemia in adults who have had at least 1 prior therapy, only if the conditions in the managed access agreement for ibrutinib are followed.
- 1.2 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

<b>Description of the technology</b>	Ibrutinib (Imbruvica, Janssen) inhibits a protein called Bruton's tyrosine kinase, stopping B-cell (lymphocyte) proliferation and promoting cell death.
<b>Marketing authorisation</b>	<p>Ibrutinib has a marketing authorisation in the UK for treating adults with Waldenstrom's macroglobulinaemia:</p> <ul style="list-style-type: none"> <li>• who have had at least 1 prior therapy, or</li> <li>• as first-line treatment in patients for whom chemo-immunotherapy is unsuitable.</li> </ul>
<b>Adverse reactions</b>	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.
<b>Recommended dose and schedule</b>	Ibrutinib is taken orally (3×140-mg capsules) once daily, until the disease progresses or there is unacceptable toxicity.
<b>Price</b>	<p>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).</p> <p>The company has agreed a patient access scheme with the Department of Health. This scheme provides 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.</p> <p>The managed access agreement agreed between the company and NHS England will replace this patient access scheme. The terms of this agreement are commercial in confidence.</p>

### 3 Evidence

- 3.1 The appraisal committee ([section 7](#)) 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

- 4.1 The appraisal committee reviewed the data available on the clinical and cost effectiveness of ibrutinib, having considered evidence on the nature of Waldenstrom's macroglobulinaemia 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 Waldenstrom's macroglobulinaemia**

- 4.2 The committee heard from the clinical experts that there is no established standard of care and no previously licensed treatments specifically for treating Waldenstrom's macroglobulinaemia. Ibrutinib is therefore the first technology with a specific licence for treating this rare condition. The committee understood that the most common options currently used for treating Waldenstrom's macroglobulinaemia are a range of single and combination therapies that were developed for treating other lymphoproliferative diseases. Common combination chemo-immunotherapies include alkylating agents (such as cyclophosphamide) or nucleoside analogues (cladribine or fludarabine), in combination with rituximab. In people for whom chemo-immunotherapy is unsuitable, treatment options include rituximab or chlorambucil. The committee heard from the patient experts that treatment options have been further limited by the removal of bortezomib from the Cancer Drugs Fund and by the restriction of funding for stem cell transplantation, which the clinical expert stated is now only available on an individual funding basis. The choice of treatment depends on the severity of the disease and on patient and clinician choice, because there is no treatment regimen that has been shown to be the most effective. The committee concluded that there is no standard of care for treating Waldenstrom's macroglobulinaemia and that treatment tends to combine rituximab with a range of chemotherapy options.

#### **Clinical need of patients with Waldenstrom's macroglobulinaemia**

- 4.3 The committee noted that Waldenstrom's macroglobulinaemia is an incurable cancer of the lymphatic system, a form of non-Hodgkin's lymphoma. It understood that Waldenstrom's macroglobulinaemia meets the European Medicines Agency's prevalence criteria for rare disease, with around

330 people in England newly diagnosed with the condition each year. It also understood that Waldenstrom's macroglobulinaemia has a long disease trajectory, with median overall survival ranging from less than 4 years to 12 years, and that nearly half of people diagnosed with Waldenstrom's macroglobulinaemia will die from causes unrelated to the disease. The committee was aware that Waldenstrom's macroglobulinaemia is associated with major disease-related symptoms such as infections, weakness, extreme fatigue and breathlessness. It also read submissions from patients, and heard the patient experts' individual personal accounts of other severe symptoms of Waldenstrom's macroglobulinaemia including severe bone, joint and eye pain. The effects of Waldenstrom's macroglobulinaemia may make normal life impossible and force people to stop working. Patients highlighted to the committee that current treatments can cause severe adverse reactions (including peripheral neuropathy and digestive tract dysfunction) that can be unbearable, and they described the particularly debilitating effects of stem cell transplantation. Even though patients may have a good response to first-line therapy, the constant threat of relapse can put a huge burden on patients and their families. The committee also heard from the patient and clinical experts that patients are restricted in the number of lines of chemotherapy they can have, because of cumulative toxicity. For people presenting with the disease at an earlier age treatment options can rapidly become exhausted, leaving no effective therapies available to them. The committee concluded that Waldenstrom's macroglobulinaemia is a rare and debilitating disease that is associated with a high unmet clinical need for new effective therapies.

- 4.4 The committee heard from the clinical experts that ibrutinib is a novel treatment with a completely different mechanism of action to existing treatments. It understood that around 90% of people with Waldenstrom's macroglobulinaemia have the MYD88 L265P somatic gene mutation with specific biological and clinical features, and that ibrutinib targets cell death in this particular mutation. The clinical experts highlighted to the committee that ibrutinib would be particularly valuable for patients with disease that was refractory to first-line treatment or who relapsed following successful first-line therapy. The committee heard from the patient experts that it is very important to have a number of lines of therapy available to postpone the point at which all treatment options are exhausted, when the outcome is likely to be death from the disease. Both the patient and clinical experts emphasised that ibrutinib is highly effective compared with existing treatments, and very well tolerated,



with a lower toxicity profile. The convenience of an oral therapy is also greatly valued by patients because it allows them to take the treatment at home, with no need for hospital visits or infusions. A patient expert further explained that they had been having ibrutinib for several years and found it to be a life-transforming drug that had dramatically improved their quality of life, allowing them to participate in general day-to-day activities and very quickly return to their normal life, including work. The effect on their Waldenstrom's macroglobulinaemia symptoms was almost immediate on starting ibrutinib, and the symptoms quickly came back if treatment was stopped. The committee concluded that the availability of a targeted, effective and well tolerated oral therapy is highly valued by patients and addresses a significant unmet need among people with Waldenstrom's macroglobulinaemia.

## Clinical trial evidence

4.5 The committee noted that the clinical evidence for ibrutinib came from one single-arm, open-label trial in the US (PCYC-1118E). This included 63 adults with Waldenstrom's macroglobulinaemia who had had at least one prior therapy. The committee understood that no clinical trial evidence had been presented for Waldenstrom's macroglobulinaemia in adults who have not had prior therapy and for whom chemo-immunotherapy is unsuitable, although it noted that the marketing authorisation does not specify prior treatment. It heard from the clinical experts that chemo-immunotherapy is more likely to be unsuitable for older people because of potential co-morbidities and the high toxicity of current treatments, and that this group of patients is therefore particularly disadvantaged. The committee also heard from the company that there is difficulty collecting data in such a small population of patients. The committee understood from the clinical experts that the ongoing iNNOVATE study of ibrutinib in combination with rituximab includes a non-randomised sub study of ibrutinib monotherapy in untreated and previously treated Waldenstrom's macroglobulinaemia that is refractory to rituximab (arm C of the trial), which will provide some data in the future. The committee appreciated that patients who have not had prior therapy and for whom chemo-immunotherapy is unsuitable have a particularly high unmet clinical need, and it considered that the current lack of trial data for this group of patients is a limitation of the evidence base.

4.6 The committee noted the ERG's comments that PCYC-1118E was generally well

reported and that, because it was an open-label single arm study without a control group, there were a number of potential biases. It also noted the ERG's comments that the outcome measures in the study were generally valid and reliable, but that the response criteria for the primary outcome were modified from internationally accepted measures. However, the committee accepted comments from the clinical experts that the response criteria used in the trial reflected clinical practice. The committee also heard from the clinical experts that the trial was generalisable to a UK clinical setting and that it was usual for patients in clinical trials to be younger and fitter than those who might routinely present in clinical practice. The committee concluded that the study was of a reasonable quality, generalisable to UK clinical practice and suitable for decision making, but was limited by the lack of a comparison against a treatment used in the UK.

## Clinical trial results

- 4.7 The committee noted that at 24-month follow up, the overall response rate in PCYC-1118E was 90.5% (95% confidence interval [CI] 80.4 to 96.4), and that median progression-free survival and overall survival had not been reached, indicating that more than 50% of patients were still alive. The committee was aware that, in response to consultation, the company had provided 37-month follow-up data on the rates of progression-free survival (82.0%, 95% CI 69.1 to 89.9) and overall survival (90.0%, 95% CI 77.4 to 95.8). In addition, early results from arm C of the iNNOVATE study at 17.1-month follow up demonstrated an overall response rate of 90% and a major response rate of 71%. The committee concluded that the results from the studies suggest that ibrutinib is associated with high response rates and high progression-free survival and overall survival rates at 2 to 3 years. However, it also concluded that the longer-term effects on progression and survival are uncertain because no data are available.

## Indirect comparison

- 4.8 The committee was aware that the company had presented an indirect comparison of ibrutinib against existing treatments for Waldenstrom's macroglobulinaemia. This used the results from a Europe-wide chart review study; a retrospective observational study that generated data on epidemiology, treatment and efficacy outcomes for treatment-naive and relapsed Waldenstrom's macroglobulinaemia patients over 10 years. The committee noted that the company had created a matched cohort to the PCYC-1118E

population by selecting a subset of the European chart-review cohort who had had similar lines of therapy to the patients in PCYC-1118E. Patients in PCYC-1118E who had 5 lines of therapy were excluded from the analysis because there were no matched patients in the European chart review. The committee understood that the analysis suggested a substantial reduction in the risk of disease progression with ibrutinib compared with existing Waldenstrom's macroglobulinaemia therapies. It was also aware that the ERG had several concerns about the company's approach, including the methods used to select patients in the matched cohort. In response to consultation, the committee heard from the company that it had taken 4 different approaches to estimating comparative effectiveness, and that all 4 methods suggested a statistically significant reduction in the risk of disease progression with ibrutinib compared with existing Waldenstrom's macroglobulinaemia therapies. The committee accepted, based on the results of the indirect comparison and the testimonies from patients and clinical experts, that ibrutinib appears to be more clinically effective than existing treatments but concluded that there remains considerable uncertainty about the size of the long-term benefit because of limitations in the data available.

## *Cost effectiveness*

### **Company's economic model**

- 4.9 The committee noted that the company had developed a Markov state transition model with 5 health states comparing ibrutinib with treatment of physician's choice to reflect the distribution of therapies used in UK clinical practice. The committee heard from the ERG that the sequencing used in the company's model was inconsistent with the data and population in PCYC-1118E and that many patients in PCYC-1118E had more than one prior therapy. The committee was mindful of the limitations of the model structure but concluded that it was acceptable for decision making.

### **Modelling mortality**

- 4.10 The committee considered the estimates of pre-progression mortality and noted the ERG's comments that the company had potentially used unsuitable data to inform the pre-progression mortality for the comparator group (physician's choice). The committee noted that, in response to consultation, the company had revised its approach to modelling pre-progression mortality for

the comparator group so that deaths occurring after patients had progressed but while they were in the 'watch and wait' period (that is, not yet started the next line of treatment) were no longer used to derive the pre-progression risk of death. The committee heard from the ERG that some uncertainty remained about whether there was an inflated risk of death prior to progression in the comparator group. However, the committee noted that the cost-effectiveness estimates were not sensitive to changes in pre-progression mortality for the comparator group and concluded that the company's revised approach was acceptable for decision making.

- 4.11 The committee noted that the company's original economic model had assumed general population mortality rates for patients on ibrutinib prior to disease progression, with the rationale that only 3 people died within the 24-month follow-up period of PCYC-1118E. The committee was aware that in response to the ERG's concerns reported in the appraisal consultation document, the company had revised its modelling approach. It now assumed a constant hazard based on PCYC-1118E data until the constant hazard crossed the general population hazard, when the general population hazard was assumed. The committee recalled that median overall survival had not been reached in PCYC-1118E and it noted comments from the clinical experts that pre-progression mortality estimates were unclear, because almost half of patients with Waldenstrom's macroglobulinaemia die from unrelated causes. In the clinical expert's view, death in the progression-free state is most likely to be from an unrelated cause. The committee also heard from the clinical experts that it was not unreasonable to expect pre-progression survival to be better in patients taking ibrutinib than other currently available alternatives, because of the greater long and short-term haematological and infectious complications of conventional chemotherapy. The committee accepted that there is uncertainty associated with estimating pre-progression mortality in the ibrutinib arm because of limitations in the data available. However, it concluded that it could accept the company's revised approach even though it might represent a 'best case' scenario.

### Most plausible incremental cost-effectiveness ratio

- 4.12 The committee noted that the company's base-case incremental cost-effectiveness ratio (ICER) incorporating the updated patient access scheme for ibrutinib and revisions to the model (see [sections 4.10 and 4.11](#)) was £54,100

per quality-adjusted life year (QALY) gained. It heard from the ERG that their amended base-case ICER (including re-estimating drug acquisition and administration costs, correcting errors on follow-up costs and using pre-progression mortality data from PCYC-1118E) was between £56,000 and £57,000 per QALY gained when incorporating the updated patient access scheme. The committee recalled its earlier conclusions (see [section 4.8](#) and [section 4.11](#)) that there is uncertainty about the size of the clinical benefit of ibrutinib compared with existing Waldenstrom's macroglobulinaemia therapies and in the modelling of pre-progression mortality. Taking into account the uncertainties identified, the committee concluded that the most plausible ICER is likely to be at least £54,100 per QALY gained as estimated in the company's base-case analysis. It further concluded that this was substantially above the range normally considered a cost-effective use of NHS resources (that is, between £20,000 and £30,000 per QALY gained).

## End-of-life considerations

4.13 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 did not consider that ibrutinib is indicated for people with a short life expectancy, noting that the estimates presented in the company's submission ranged from less than 4 years to 12 years and that median overall survival in the Europe-wide chart review study was 123 months. The committee also considered that it is currently unknown whether ibrutinib offers an extension to life of at least an additional 3 months compared with current NHS treatment, but noted that it did not need to reach a conclusion on this point because the first criterion of life expectancy less than 24 months was not met. The committee concluded that ibrutinib did not meet the criteria to be considered a life-extending, end-of-life treatment.

## Innovation

4.14 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 Waldenstrom's macroglobulinaemia. 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.

## Cancer Drugs Fund

- 4.15 The committee considered whether it would be appropriate to recommend ibrutinib for inclusion in the 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 to be cost-effective, and if it is possible that the clinical uncertainty can be addressed through collection of outcome data from patients treated in the NHS, normally within 2 years.
- 4.16 The committee considered whether clinical uncertainty associated with ibrutinib could be addressed through collection of additional data. It understood that interim results from the ongoing iNNOVATE trial are expected in 2017 and that longer follow-up data will become available from PCYC-1118E. It also understood that the company intends to collect additional efficacy and resource-use data as an add-on to an existing national registry of people with Waldenstrom's macroglobulinaemia. The committee welcomed the efforts being made to collect data on this rare condition and its treatment. It heard from the clinical experts that the registry currently includes over 300 patients and is able to record patient-level data on progression, survival, response, quality of life, and genomic markers, both for treatment-naïve and previously treated people with Waldenstrom's macroglobulinaemia. The committee considered that this data would be a valuable addition to the clinical evidence base and may resolve some of the uncertainties identified.
- 4.17 The committee considered whether the ICERs presented for ibrutinib had the plausible potential to be cost-effective in routine use. It recalled its earlier conclusion that the most plausible ICER is likely to be at least £54,100 per QALY gained, which is substantially above the level considered to be a cost-effective use of NHS resources (that is, between £20,000 and £30,000 per QALY gained). It considered that at this level the ICER did not have the plausible potential to be cost effective in routine use. However the committee heard from the company that it had made an offer to provide ibrutinib at a price that resulted in ibrutinib being cost-effective within the Cancer Drugs Fund. Furthermore, the committee heard that the company was committed to exploring mechanisms for providing

ibrutinib at a cost-effective price when it is re-appraised by NICE upon its exit from the Cancer Drugs Fund. The committee concluded that it would be able to recommend ibrutinib as an option for use within the Cancer Drugs Fund for treating Waldenstrom's macroglobulinaemia provided that a managed access agreement was in place that allowed ibrutinib to be used cost-effectively within the Cancer Drugs Fund. The committee considered what additional data could be collected to resolve some of the clinical uncertainties it had highlighted (see [section 4.11](#)). It agreed that overall survival data could be collected using the Systemic Anti-Cancer Therapy dataset, which could address uncertainty in pre-progression mortality for those receiving ibrutinib. The committee also expressed interest in seeing updated efficacy data from Study 1118E and INNOVATE (arm C). The committee concluded that further data collection could resolve some of the clinical uncertainties in the evidence base.

### *Potential equality issues*

- 4.18 The committee noted the potential equality issue raised by the company and the clinical experts that Waldenstrom's macroglobulinaemia is a condition with a greater prevalence in older people. It heard from the patient experts that existing treatments for Waldenstrom's macroglobulinaemia have high levels of toxicity and adverse reactions and that these are less likely to be tolerated by older people. The committee acknowledged that access to ibrutinib may be particularly beneficial for older people.

### *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

TA491	Appraisal title: Ibrutinib for treating Waldenstrom's macroglobulinaemia	Section
<b>Key conclusion</b>		
<p>Ibrutinib is recommended for use in the Cancer Drugs Fund as an option for treating Waldenstrom's macroglobulinaemia in adults who have had at least 1 prior therapy, only if the conditions in the managed access agreement for ibrutinib are followed.</p> <p>The committee considered that the most plausible incremental cost-effectiveness ratio (ICER) is likely to be at least £54,100 per quality-adjusted life year (QALY) gained and noted that this is substantially above the level considered to be a cost-effective use of NHS resources (that is, between £20,000 and £30,000 per QALY gained).</p> <p>The committee heard from the company that it had made an offer to provide ibrutinib at a price that resulted in ibrutinib being cost-effective within the Cancer Drugs Fund. Furthermore, the committee heard that the company was committed to exploring mechanisms for providing ibrutinib at a cost-effective price when it is re-appraised by NICE upon its exit from the Cancer Drugs Fund. The committee concluded that it would be able to recommend ibrutinib as an option for use within the Cancer Drugs Fund for treating Waldenstrom's macroglobulinaemia provided that a managed access agreement was in place that allowed ibrutinib to be used cost-effectively within the Cancer Drugs Fund.</p>		1.1, 4.17
<b>Current practice</b>		
Clinical need of patients, including the availability of alternative treatments	The committee concluded that there is no standard of care for treating Waldenstrom's macroglobulinaemia and that targeted therapy is highly valued by patients and addresses a significant unmet need.	4.2, 4.4
<b>The technology</b>		



<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The committee understood that around 90% of people with Waldenstrom's macroglobulinaemia have the MYD88 L265P somatic gene mutation with specific biological and clinical features, and that ibrutinib targets cell death in this particular mutation.</p> <p>The committee accepted that ibrutinib has several benefits for people including oral administration, manageable adverse reactions and low toxicity. It concluded that ibrutinib could be considered a step change in managing Waldenstrom's macroglobulinaemia.</p>	<p>4.4, 4.14</p>
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>The committee heard that ibrutinib would be particularly valuable for people with disease that is refractory to first-line treatment or who relapsed following successful first-line therapy.</p>	<p>4.4</p>
<p>Adverse reactions</p>	<p>The committee concluded that ibrutinib is a well-tolerated therapy.</p>	<p>4.4</p>
<p><b>Evidence for clinical effectiveness</b></p>		

<p>Availability, nature and quality of evidence</p>	<p>The committee understood that the study PCYC-1118E was generally well reported but there were a number of potential biases because this was an open-label single arm study without a control group.</p> <p>The committee understood that no clinical trial evidence had been presented for Waldenstrom's macroglobulinaemia in adults who have not had prior therapy and for whom chemo-immunotherapy is unsuitable. The committee appreciated that patients who have not had prior therapy and for whom chemo-immunotherapy is unsuitable have a particularly high unmet clinical need and it considered that the current lack of trial data for this group of patients was a limitation of the evidence base.</p> <p>The committee was aware that the company had presented an indirect comparison of ibrutinib against existing treatments for Waldenstrom's macroglobulinaemia. This used the results from a Europe-wide chart review study; a retrospective observational study that generated data on epidemiology, treatment and efficacy outcomes for treatment-naive and relapsed Waldenstrom's macroglobulinaemia patients over 10 years.</p>	<p>4.5, 4.6, 4.8</p>
<p>Relevance to general clinical practice in the NHS</p>	<p>The committee concluded that PCYC-1118E is of a reasonable quality, generalisable to UK clinical practice and suitable for decision making, but is limited by the lack of a comparison against a treatment used in the UK.</p>	<p>4.6</p>
<p>Uncertainties generated by the evidence</p>	<p>The committee concluded that the longer term effects of ibrutinib on progression and survival are uncertain because no data is available.</p> <p>The committee was aware that the company's indirect comparison suggested a substantial reduction in the risk of disease progression with ibrutinib compared with existing Waldenstrom's macroglobulinaemia therapies but that the ERG had a number of concerns with the company's approach. It accepted, based on the results of the indirect comparison and the testimonies from patients and clinical experts, that ibrutinib appears to be more clinically effective than existing treatments but there is considerable uncertainty about the size of the long-term benefit because of limitations in the data available.</p>	<p>4.7, 4.8</p>

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	No clinically relevant subgroups were identified.	-
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee concluded that the results from PCYC-1118E suggest that treatment with ibrutinib is associated with high response rates (90.5%) and high progression-free survival and overall survival rates (82.0% and 90.0%) at 3 years.	4.7
<b>Evidence for cost effectiveness</b>		
Availability and nature of evidence	The committee understood that the company's model included patients with relapsed or refractory Waldenstrom's macroglobulinaemia who had had one prior therapy. The committee was mindful of the limitations within the model structure but concluded that it was acceptable for decision making.	4.9
Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee concluded that there is considerable uncertainty about the size of the long-term benefit of ibrutinib because of limitations in the data available.  The committee accepted that there is uncertainty associated with estimating pre-progression mortality in the ibrutinib arm because of limitations in the data available.	4.8, 4.11

<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>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?</p>	<p>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.</p>	<p>4.14</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>The committee made no specific recommendations for any subgroups.</p>	<p>-</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The committee concluded that the company's approach was likely to represent a 'best case' scenario and that a less favourable mortality rate would lead to a higher ICER than the one presented in the company's base case.</p>	<p>4.11</p>
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The committee concluded that the most plausible ICER is likely to be at least £54,100 per QALY gained as estimated in the company's base-case analysis.</p>	<p>4.12</p>

<b>Additional factors taken into account</b>		
Cancer Drugs Fund	The committee heard from the company that it had made an offer to provide ibrutinib at a price that resulted in ibrutinib being cost-effective within the Cancer Drugs Fund. Furthermore, the committee heard that the company was committed to exploring mechanisms for providing ibrutinib at a cost-effective price when it is re-appraised by NICE upon its exit from the Cancer Drugs Fund. The committee concluded that it would be able to recommend ibrutinib as an option for use within the Cancer Drugs Fund for treating Waldenstrom's macroglobulinaemia provided that a managed access agreement was in place that allowed ibrutinib to be used cost-effectively within the Cancer Drugs Fund.	4.17
Patient access schemes (PPRS)	The company has agreed a patient access scheme with the Department of Health. The level of the discount increased during the appraisal and is commercial in confidence. The managed access agreement agreed between the company and NHS England will replace this patient access scheme. The terms of this agreement are commercial in confidence.	4.19
End-of-life considerations	The committee concluded that ibrutinib did not meet the criteria to be considered a life-extending, end-of-life treatment.	4.13
Equalities considerations and social value judgements	The committee acknowledged that access to ibrutinib may be particularly beneficial for older people.	4.18

## 5 Implementation

- 5.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available within the conditions of the managed access agreement. This means that, if a patient has Waldenstrom's macroglobulinaemia and the doctor responsible for their care thinks that ibrutinib is the right treatment, it should be available for use, in line with NICE's recommendations and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England's [Appraisal and Funding of Cancer Drugs from July 2016 \(including the new Cancer Drugs Fund\) – a new deal for patients, taxpayers and industry](#).
- 5.2 Ibrutinib has been recommended according to the conditions in the managed access agreement. As part of this, NHS England and Janssen have agreed a commercial access agreement that makes ibrutinib available to the NHS at a reduced cost. The financial terms of the agreement are commercial in confidence. Any enquiries from NHS organisations about the commercial access agreement should be directed to Janssen Customer Services on 0149 456 7400 or [janssenukcustomerservices@its.jnj.com](mailto:janssenukcustomerservices@its.jnj.com).

## **6 Recommendation for data collection**

- 6.1 As a condition of the positive recommendation and the managed access arrangement, the company is required to collect updated efficacy data from the PCYC-1118E and iINNOVATE studies.

## 7 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.

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Technical Adviser

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Project Manager

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## Accreditation

