The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using venetoclax 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 expert and patient expert.

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 venetoclax 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: 8 March 2017

Second appraisal committee meeting: 16 March 2017

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

1.1 Venetoclax is not recommended within its marketing authorisation for treating chronic lymphocytic leukaemia in adults:

- who have a 17p deletion or TP53 mutation and who are unsuitable for, or whose disease has progressed after, a B-cell receptor pathway inhibitor or
- without a 17p deletion or TP53 mutation, and whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor.

1.2 This guidance is not intended to affect the position of patients whose treatment with venetoclax 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 | Venetoclax (Venclyxto, AbbVie) is a selective small molecule inhibitor of B-cell lymphoma 2, an anti-apoptotic protein overexpressed in around 95% of people with chronic lymphocytic leukaemia. |
| Marketing authorisation | Venetoclax is licensed for ‘the treatment of chronic lymphocytic leukaemia (CLL) in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor’ and for ‘the treatment of CLL in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor.’ |
| Adverse reactions | There is a risk of tumour lysis syndrome during the initial 5-week dose-titration phase of treatment because venetoclax can cause rapid tumour reduction. Grade 3 or 4 neutropenia has also been reported in patients treated with venetoclax. For full details of adverse reactions and contraindications, see the summary of product characteristics. |
### Recommended dose and schedule

<table>
<thead>
<tr>
<th></th>
<th>The starting dose is 20 mg once daily for 7 days. The dose must be gradually increased over 5 weeks up to the recommended daily dose of 400 mg. For full details of the dose increase schedule, see the summary of product characteristics.</th>
</tr>
</thead>
</table>

### Price

<table>
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<tr>
<th></th>
<th>A 112-pack of 100 mg tablets (which is enough for 28 days of 400 mg treatment, used at week 5 onward) costs £4,789.47 (excluding VAT). Costs may vary in different settings because of negotiated procurement discounts.</th>
</tr>
</thead>
</table>

### 3 Evidence

The appraisal committee (section 6) considered evidence submitted by AbbVie 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 venetoclax, having considered evidence on the nature of chronic lymphocytic leukaemia (CLL) and the value placed on the benefits of venetoclax by people with the condition, those who represent them and clinical experts. It also took into account the effective use of NHS resources.

#### Symptoms and management of CLL

4.1 The committee was aware that CLL is frequently associated with fatigue and recurrent infections. It understood that patients and their families can become isolated to protect themselves from infection, which stops people from living a normal life. The committee also heard that patients spend a long time in the ‘watch and wait’ stage of the treatment pathway, anticipating relapse which can have a severe psychological effect on people living with the disease.
Current treatment

4.2 The committee heard from the patient and clinical experts that current treatments are associated with several adverse reactions, and that because many people diagnosed with CLL are older and may have co-morbidities, many of these treatments are often not tolerated. The clinical expert highlighted that there is often a trade-off between efficacy and the adverse reactions associated with a particular treatment and that patient choice is important in selecting an appropriate therapy. The clinical expert stated that, once treatment options have been exhausted, prognosis is poor. The committee understood the importance of having different options available for treating CLL.

Patient populations

4.3 The committee considered the groups of people with CLL included in the marketing authorisation for venetoclax. These were adults with CLL:

- with a 17p deletion or TP53 mutation and who are unsuitable for, or whose disease has progressed after, a B-cell receptor pathway inhibitor, or
- without a 17p deletion or TP53 mutation and whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor.

The committee discussed the population with a 17p deletion or TP53 deletion who are unsuitable for a B-cell receptor pathway inhibitor. The committee was aware that this group of people could either have received no previous therapy or they may have had chemo-immunotherapy. The committee noted that none of the venetoclax clinical trials defined unsuitability for a B-cell receptor pathway inhibitor. The committee heard from the clinical expert that in clinical practice, ‘unsuitable’ is defined as intolerance and that there are few, if any, people who are intolerant to both of the B-cell receptor pathway inhibitors recommended by NICE (idelalisib and ibrutinib) because of their different safety profiles. The
committee concluded that the population in the marketing authorisation for whom a B-cell receptor pathway inhibitor is unsuitable was unlikely to be relevant to clinical practice in England.

The committee discussed the population who had a 17p deletion or TP53 mutation and whose disease progressed after a B-cell receptor pathway inhibitor and the population without a 17p deletion or TP53 mutation and whose disease has progressed following both chemo-immunotherapy and a B-cell receptor pathway inhibitor. The clinical expert stated that both populations were relevant to clinical practice in England, and that both populations had limited treatment options.

The clinical expert further explained that although 17p deletion or TP53 mutation can predict poorer prognosis, clinical decisions once the disease has progressed after 1 or more therapies are based on length of response rather than on deletion or mutation status. The committee considered this but concluded that it should follow the marketing authorisation for venetoclax, which separated the populations by the presence or absence of the 17p deletion or TP53 mutation.

The committee concluded that, based on current clinical practice, venetoclax would be used in the populations defined in the marketing authorisation as having disease progression after therapy (that is after a B-cell receptor pathway inhibitor or after both chemo-immunotherapy and a B-cell receptor pathway inhibitor), and that overall it was not persuaded of the relevance of the population who was unsuitable for a B-cell receptor pathway inhibitor to clinical practice in England.

**Comparators**

4.4 The company presented analyses for venetoclax compared with best supportive care and palliative care. The company defined best supportive care as rituximab and high-dose methylprednisolone and it defined palliative care as no active treatment. The clinical expert explained that in
clinical practice, palliative care would be an option for very few people because they would generally be offered therapy such as alemtuzumab or rituximab. The committee concluded that best supportive care was a more appropriate comparator than no intervention (what the company defined as palliative care), and that the company’s use of best supportive care was an acceptable basis for its decision-making.

Clinical effectiveness

4.5 The committee noted that the clinical evidence for venetoclax came from 1 phase I and 2 phase II, single-arm trials.

- The M12-175 phase I trial recruited patients with and without a 17p deletion or TP53 mutation (n=67). Median progression-free survival was 41.4 months. Overall survival cannot be reported here because it is considered confidential by the company.
- The M13-982 phase II trial recruited only patients with a 17p deletion or TP53 mutation and relapsed or refractory CLL after at least 1 previous therapy (n=158). Median progression-free survival was 27.2 months. After 12 months, 86.5% of people were alive.
- The M14-032 phase II trial recruited patients with or without a 17p deletion or TP53 mutation, who had relapsed or refractory CLL after a B-cell receptor pathway inhibitor (either ibrutinib [n=43] or idelalisib [n=21]). Median progression-free survival was not reached, but after 12 months 88.1% of patients in the prior ibrutinib arm and 95.2% of patients in the prior idelalisib arm were still alive.

4.6 The committee noted that the company’s clinical-effectiveness analyses were based on the intention-to-treat populations in each of the trials. This meant that the analyses of M12-175 and M14-032 included patients with and without a 17p deletion or TP53 mutation. In addition, although M13-982 only recruited people with a 17p deletion or TP53 mutation, the analyses included both people considered unsuitable for a B-cell receptor pathway inhibitor and people whose disease had progressed after a B-cell
receptor pathway inhibitor. The committee agreed that this made it difficult to interpret how these results related to each of the relevant populations (section 4.3).

4.7 The committee was concerned that the single-arm design of the trials meant that the results were potentially biased, and that the trials included relatively few patients. Furthermore, only 18 patients in M13-982 had disease progression after a B-cell receptor pathway inhibitor (the population with a 17p deletion or TP53 mutation considered relevant to clinical practice). The committee noted comments from the clinical expert that venetoclax appears to be an effective therapy for people with few alternative treatment options but it concluded there was a large degree of uncertainty in the clinical evidence.

Generalisability of the results

4.8 The committee was concerned about how generalisable the results of the clinical trials were to clinical practice in England, given that neither M12-175 nor M14-032 included any UK centres. The committee also understood that the trials recruited people with an Eastern Cooperative Oncology Group (ECOG) performance status score of less than 2, corresponding to a population whose activities are relatively unrestricted by their disease. It questioned whether this was reflective of patients for whom venetoclax was likely to be an option in clinical practice in England, given that there are few treatments available to people after a B-cell receptor pathway inhibitor. The clinical expert stated that people with relapsed or refractory disease after a B-cell receptor pathway inhibitor are likely to have a higher ECOG score, reflecting an increased disease burden. The committee concluded that people enrolled in the venetoclax clinical trials were likely to have a lower burden of disease than the people for whom venetoclax would be an option in England, and that the treatment benefit for these people was therefore uncertain.
Adverse reactions to venetoclax treatment

4.9 Venetoclax is associated with potentially serious adverse reactions such as tumour lysis syndrome, a consequence of rapid cell death. The clinical expert explained that the 5-week dose escalation schedule helps to prevent this and noted that there had been very few clinical cases of tumour lysis syndrome in the venetoclax trials. The committee acknowledged the risks associated with venetoclax treatment but concluded that it presented an acceptable safety profile.

Indirect comparison with best supportive care

4.10 The committee noted that because venetoclax had only been studied in single-arm trials, in order to proceed with the economic modelling the company compared the pooled outcomes for venetoclax with best supportive care. The survival outcomes for best supportive care came from the rituximab arm of the 116 randomised control trial, which compared idelalisib with rituximab for CLL.

4.11 In order to maximise the limited data from the venetoclax trials, the company pooled the data from the M12-175, M13-982 and M14-032 trials. The evidence review group (ERG) explained that the company combined patient data from multiple studies as if they belonged to a single study, despite differences in baseline characteristics. In addition, the pooling included data from safety expansion cohorts meaning that patients would have had venetoclax for different amounts of time. However, the committee noted that the ERG’s preferred method of pooling the data through a meta-analysis produced similar results to the company’s analysis. The committee concluded that although imperfect, the company’s pooling of the data from the venetoclax studies was acceptable.

4.12 The company’s comparison of the pooled venetoclax data with the best supportive care data showed that overall survival was much higher with venetoclax. However, for patients both with and without a 17p deletion or
TP53 mutation, the committee noted that the comparison was flawed. Firstly, the rituximab arm of the 116 trial was composed entirely of patients eligible for idelalisib, whereas the indication for venetoclax is disease progression after idelalisib (or ibrutinib). Secondly, the venetoclax trial populations and the population from the 116 trial had not been matched for baseline characteristics. Importantly, a higher proportion of patients in the 116 trial had Rai stage 3 or 4 disease than in the venetoclax trials, suggesting that patients in the 116 trial had more advanced disease than those in the venetoclax trials. The committee concluded that patients in the rituximab arm of the 116 trial were likely to have a lower overall survival than would be expected if the venetoclax trial patients had received best supportive care. The committee concluded that the relative survival benefit of venetoclax compared with best supportive care was likely to be biased in favour of venetoclax.

Cost effectiveness

The committee discussed the company’s economic model and modelling assumptions. The company modelled the 2 populations as defined in the marketing authorisation (section 4.3). The committee was aware that this included people unsuitable for a B-cell receptor pathway inhibitor and that the committee had not been persuaded of the relevance of this population to clinical practice in England (section 4.3). The committee noted that the model structure was similar to models used in previous NICE technology appraisals and concluded it was appropriate for its decision-making.

Venetoclax overall and progression-free survival extrapolations

The committee considered the company’s extrapolation of data from the pooled venetoclax trials, noting that it had chosen a Weibull distribution based on visual inspection of the extrapolated curves and goodness of fit statistics. However, the committee was aware that while all of the distributions fitted the observed data well, beyond the 4 years of observed data the curves diverged greatly. The committee noted that based on
visual inspection of the plots of the hazard functions, a Gompertz
distribution could fit the data equally well. The committee was concerned
that an extrapolation based on the Gompertz distribution resulted in lower
survival outcomes than those based on the Weibull, and that the choice of
distribution was therefore an important driver of the model. The clinical
expert explained that the predicted 10-year survival rate from the Weibull
extrapolation was more clinically plausible than that from the Gompertz
extrapolation. The committee concluded that despite the uncertainty, the
company’s use of the Weibull distribution for the survival extrapolation
was justifiable.

Source of best supportive care data

4.15 The committee recalled that the company chose the rituximab arm of the
116 trial as its source of best supportive care data. The committee heard
from the ERG that this was not appropriate, because patients in the
rituximab arm did not have relapsed or refractory disease after having a
B-cell receptor pathway inhibitor: they had been randomised to have
rituximab rather than a B-cell receptor pathway inhibitor. The ERG
preferred to use the post-progression survival data from the idelalisib arm
of the 116 trial, because these patients all had disease progression after a
B-cell receptor pathway inhibitor. The committee agreed that this
population more closely matched the population that would be offered
venetoclax.

4.16 The clinical expert explained that survival for people whose disease has
progressed would be similar regardless of previous treatment, and so
post-progression survival after venetoclax would be expected to be similar
to overall survival for best supportive care. The committee noted that the
post-progression survival of people having venetoclax was more similar to
that of people whose disease had progressed after idelalisib in the 116
trial than the overall survival from the rituximab arm of the trial. The
committee concluded that this further strengthened the case for the ERG’s
choice of best supportive care data from the idelalisib arm of the 116 trial.
4.17 The committee preferred the ERG’s choice of best supportive care data from the idelalisib arm of the 116 trial but it acknowledged that other sources of data were available, such as post-progression survival after ibrutinib from the RESONATE trial. In addition, the committee was concerned that whatever the source of data, the comparisons would be naive and potentially subject to bias. For example, from the baseline characteristics data, patients in the idelalisib study (116 trial) appear to have more advanced disease than those in the venetoclax trials (section 4.12). The committee would have preferred to see an indirect comparison that attempted to match the characteristics of the patients in the venetoclax trials to more similar patients, using for example the haematological malignancies research network database.

Utility values

4.18 The committee noted that the company used a value of 0.853 for the progression-free survival health state based on pooled data from the venetoclax trials. However, the ERG explained that when matched for patient age in the venetoclax trials, this value was higher than the corresponding value for the general population. The ERG chose a value of 0.71 based on progression-free survival in the second-line treatment setting from the literature. The committee concluded that it was implausible that people with CLL would have a higher quality of life than people of the same age without the disease, and that the ERG’s value was more appropriate.

Adverse event disutility and costs

4.19 The committee noted that the company had not included disutility for adverse events in its base-case. The committee was aware that the ERG’s base-case did include disutility for adverse events, and also updated the costs of some adverse events using more recent data. The committee concluded that it preferred the ERG’s approach, although
neither change had a large effect on the costs or quality-adjusted life years (QALYs).

Cost-effectiveness results

4.20 For adults with a 17p deletion or TP53 mutation and who are unsuitable for, or whose disease has progressed after, a B-cell receptor pathway inhibitor, the deterministic incremental cost-effectiveness ratios (ICERs) for venetoclax compared with best supportive care were higher than the normally acceptable maximum ICER range of £20,000–30,000 per QALY gained usually considered to represent a cost-effective use of NHS resources.

4.21 For adults without a 17p deletion or TP53 mutation, and whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor, the deterministic ICERs for venetoclax compared with best supportive care were higher than the normally acceptable maximum ICER range of £20,000–30,000 per QALY gained usually considered to represent a cost-effective use of NHS resources.

4.22 The committee noted that the company had provided probabilistic ICERs, whereas in its scenario analyses the ERG had not. The ERG explained that this was because the company’s probabilistic and deterministic ICERs were similar. However, the committee did not consider them to be similar and would have preferred to use probabilistic ICERs as the basis of its decision-making.

4.23 The committee preferred the ERG’s base-case analyses as it incorporated the committee’s preferred assumptions. Specifically, the ERG adapted the company’s model to:

- use post-progression survival data after idelalisib as the source for best supportive care survival
- use a progression-free survival utility value of 0.710 rather than 0.853
- incorporate disutility and use more current costs for adverse events.
4.24 Taken together, the ERG’s changes increased the deterministic ICERs for both adults with a 17p deletion or TP53 mutation and adults without a 17p deletion or TP53 mutation.

4.25 The committee noted that although these ICERs reflected its preferred modelling assumptions, there were other plausible sources of post-progression data available that could be used as an estimate of best supportive care survival. The committee considered an ERG scenario analysis for the population with a 17p deletion or TP53 mutation, which used post-progression data after ibrutinib from the RESONATE trial as the source of best supportive care data. This increased the deterministic ICER further still. The committee therefore concluded that the ERG’s base-case ICERs represented the lower end of the range of plausible ICERs, with the true ICERs potentially much higher.

**Innovation**

4.26 The committee discussed whether it considered venetoclax to be innovative. It heard from both the patient and clinical experts that venetoclax was an important new option for CLL and patients valued its being an oral treatment. The committee also heard that some of the benefits of venetoclax may not have been captured in the modelling, such as how it improves the productivity of working-age people with CLL. However, the committee agreed that such benefits were outside of the NICE reference case and that there were no relevant additional benefits that had not been captured in the QALY.

**End of life**

4.27 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.

4.28 The committee considered the short life expectancy criterion: that is, whether the patient groups with CLL included in this appraisal would
normally live less than 24 months. The committee considered the cumulative overall survival outcomes from the company’s and ERG’s economic models. For the company’s choice of best supportive care data, the mean overall survival was less than 24 months for both people with and without a 17p deletion or TP53 mutation. From the ERG’s model using the post-progression data from the idelalisib arm of the 116 trial, mean overall survival was less than 24 months for the population with a 17p deletion or TP53 mutation population, but just over 4 years for the population without a 17p deletion or TP53 mutation. The committee noted that in both the idelalisib and ibrutinib appraisals, the committees had concluded that the end-of-life criteria were met for both the populations with and without a 17p deletion or TP53 mutation. Because venetoclax is likely to be an option for people at a later stage in the disease than the people considered in these previous appraisals, the committee, while accepting the ERG’s comparator modelling to match the venetoclax population, questioned the applicability of the ERG’s overall survival figure for people in England eligible for venetoclax. The clinical expert agreed that they would not expect people whose disease had progressed after a B-cell receptor pathway inhibitor to live longer than 24 months, even if they did not have a 17p deletion or TP53 mutation. The committee concluded that the criterion for short life expectancy was met.

4.29 The committee discussed whether venetoclax extended life by an average of at least 3 additional months. It noted that both the company’s and ERG’s modelling suggested that venetoclax was associated with a gain in overall survival of over 3 months irrespective of the choice of best supportive care data. The committee concluded that this was likely to be the case, even if life expectancy were lower than that estimated in the ERG’s model.

4.30 The committee concluded that venetoclax met both the end-of-life criteria for both the populations with and without a 17p deletion or TP53 mutation. However, the ICERs based on the committee’s preferred assumptions
were higher than those usually considered a cost-effective use of NHS resources for end-of-life treatments. The committee therefore did not recommend venetoclax for adults with CLL who have a 17p deletion or TP53 mutation and who are unsuitable for or whose disease has progressed after, a B-cell receptor pathway inhibitor or for adults with CLL without a 17p deletion or TP53 mutation, and whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor.

**Cancer Drugs Fund considerations**

4.31 The committee was aware of the new arrangements for the Cancer Drugs Fund recently agreed by NICE and NHS England. Under the new arrangements, drugs may be given a conditional recommendation by NICE and made available to NHS patients through the Cancer Drugs Fund. Such a drug will remain available within the Cancer Drugs Fund, normally for up to 2 years, while the company gathers more evidence. The committee considered that venetoclax does not have plausible potential to be cost effective for either population in its marketing authorisation. The committee also heard from the company that it would need to have further internal discussions before deciding whether to submit a case to include venetoclax in the Cancer Drugs Fund. For these reasons, the committee decided not to recommend venetoclax’s inclusion in the Cancer Drugs Fund at this stage.

**Summary of appraisal committee’s key conclusions**

<table>
<thead>
<tr>
<th>TAXXX</th>
<th>Appraisal title: venetoclax for treating chronic lymphocytic leukaemia</th>
<th>Section</th>
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<tbody>
<tr>
<td>Key conclusion</td>
<td>Venetoclax is not recommended within its marketing authorisation for treating chronic lymphocytic leukaemia (CLL) in adults:</td>
<td>1.1</td>
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</table>
• who have a 17p deletion or TP53 mutation and who are unsuitable for, or whose disease has progressed after, a B-cell receptor pathway inhibitor or
• without a 17p deletion or TP53 mutation, and whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor.

The committee concluded that in clinical practice, venetoclax would mainly be used for adults with CLL who had a 17p deletion or TP53 mutation and whose disease progressed after a B-cell receptor pathway inhibitor or adults with CLL without a 17p deletion or TP53 mutation and whose disease has progressed following both chemo-immunotherapy and a B-cell receptor pathway inhibitor.

The committee agreed that there was substantial uncertainty related to evidence base. The committee was concerned how the population in the venetoclax trials reflected those seen in clinical practice in England, that the single-arm design of the venetoclax trials meant that the results were potentially biased and that the trials included relatively few people.

In addition, the committee had concerns about the source of the data for the comparator of best supportive care. The company did not present analyses using an appropriate source of data for the comparator, as the patients in the comparator trial did not reflect those for whom venetoclax may be option. The ERG provided analyses using an alternative data source which better reflected the population in whom venetoclax is likely to be used. The committee preferred this data source, but agreed that the comparison was still subject to bias because the patients in the comparator trial appear to have more advanced disease than those in the venetoclax trials.

4.3
4.6, 4.7, 4.8
4.15, 4.17
Although the committee agreed that the end-of-life criteria were met, the ERG’s base-case ICERs were higher than the range usually considered to be a cost-effective use of NHS resources for end-of-life treatments.

**Current practice**

<table>
<thead>
<tr>
<th>Clinical need of patients, including the availability of alternative treatments</th>
<th>The committee heard that current treatments are associated with adverse reactions, and that because many people diagnosed with CLL are older and may have co-morbidities, many of these treatments are often not tolerated. The clinical expert stated that, once treatment options have been exhausted, prognosis is poor.</th>
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</table>

**The technology**

<table>
<thead>
<tr>
<th>Proposed benefits of the technology</th>
<th>The committee heard from the clinical expert that venetoclax appears to be an effective therapy for people with few alternative treatment options. The committee heard from the patient expert that they valued the fact that venetoclax was an oral treatment.</th>
</tr>
</thead>
</table>
| What is the position of the treatment in the pathway of care for the condition? | The committee heard that venetoclax was likely to be used in clinical practice in patients:  
- With a 17p deletion or TP53 mutation and whose disease has progressed after a B-cell receptor pathway inhibitor  
- Without a 17p deletion or TP53 mutation and whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor | 4.3 |
| Adverse reactions | There is a risk of tumour lysis syndrome during the initial 5-week dose-titration phase of treatment because venetoclax can cause rapid tumour reduction. Grade 3 or 4 neutropenia has also been reported in patients treated with venetoclax. | 2 |

**Evidence for clinical effectiveness**

| Availability, nature and quality of evidence | The committee noted that the clinical evidence for venetoclax came from single-arm, phase I and phase II trials with relatively few patients, meaning that the results were potentially biased.  
In addition, the results were based on the intention-to-treat populations in each of the trials making it difficult to interpret how these results related to each of populations relevant to clinical practice in England. | 4.5, 4.7 |
|  |  | 4.6 |
| Relevance to general clinical practice in the NHS | The committee was concerned that the results of the clinical trials may not be generalisable to clinical practice in England, given that only 1 of them included UK centres. The committee questioned whether the patients recruited to the venetoclax trials were reflective of the patients for whom venetoclax was likely to be an option in clinical practice in England. The committee concluded that the people in the venetoclax clinical trials were likely to have a lower burden of disease than the people for whom venetoclax would be an option in England, and that the treatment benefit in these people was therefore uncertain. | 4.8 |
### Uncertainties generated by the evidence

The committee agreed that the venetoclax trial results were uncertain.

Because venetoclax had only been studied in single-arm trials, the company conducted a naive comparison of the pooled outcomes for venetoclax with best supportive care.

The committee agreed that the comparator population did not match that in the venetoclax trials because the population were eligible for a B-cell receptor inhibitor, whereas to be offered venetoclax people must have disease progression after a B-cell receptor inhibitor. Furthermore, more patients in the comparator trial had more advanced disease than in the venetoclax trials. The committee agreed that because of these 2 issues, the relative survival benefit of venetoclax compared with best supportive care was likely to be biased in favour of venetoclax.

### Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?

There are no clinically relevant subgroups for which there is evidence of differential effectiveness.

<table>
<thead>
<tr>
<th>Uncertainties generated by the evidence</th>
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<th>4.5, 4.6, 4.7</th>
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<tr>
<td></td>
<td>Because venetoclax had only been studied in single-arm trials, the company conducted a naive comparison of the pooled outcomes for venetoclax with best supportive care.</td>
<td>4.10</td>
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<tr>
<td></td>
<td>The committee agreed that the comparator population did not match that in the venetoclax trials because the population were eligible for a B-cell receptor inhibitor, whereas to be offered venetoclax people must have disease progression after a B-cell receptor inhibitor. Furthermore, more patients in the comparator trial had more advanced disease than in the venetoclax trials. The committee agreed that because of these 2 issues, the relative survival benefit of venetoclax compared with best supportive care was likely to be biased in favour of venetoclax.</td>
<td>4.12</td>
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<tr>
<td>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</td>
<td>There are no clinically relevant subgroups for which there is evidence of differential effectiveness.</td>
<td>-</td>
</tr>
<tr>
<td>Estimate of the size of the clinical effectiveness including strength of supporting evidence</td>
<td>The comparison of the pooled venetoclax data with the best supportive care data showed that overall survival was much higher with venetoclax. However, the committee concluded that this comparison was flawed and the relative survival benefit of venetoclax compared with best supportive care was likely to be biased in favour of venetoclax.</td>
<td>4.12</td>
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<tr>
<td>Evidence for cost effectiveness</td>
<td><strong>Availability and nature of evidence</strong></td>
<td><strong>The company modelled the 2 populations as defined in the marketing authorisation. The committee noted that the model structure was similar to models used in previous NICE technology appraisals and was appropriate for its decision-making.</strong></td>
</tr>
<tr>
<td>Uncertainties around and plausibility of assumptions and inputs in the economic model</td>
<td>The comparator population did not match that in the venetoclax trials as the population were eligible for a B-cell receptor inhibitor, whereas to be offered venetoclax people must have disease progression after a B-cell receptor inhibitor. The ERG used an alternative data source: patients with disease which has progressed after a B-cell receptor pathway inhibitor. Although the committee agreed that this more appropriately matched the population that would be offered venetoclax, the committee continued to be concerned that the patients in the comparator trial were likely to have more advanced disease than those in the venetoclax trials.</td>
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<td>4.15</td>
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<td>Question</td>
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<td>Incorporation of health-related quality-of-life benefits and utility values</td>
<td>The company used pooled utility data from the venetoclax trials. However, the committee was concerned that when matched for patient age in the venetoclax trials, the company’s utility value for progression-free survival (0.853) was higher than the corresponding value for the general population. The committee preferred a value of 0.71 based on progression-free survival in the second-line treatment setting from the literature. The committee heard that some of the benefits of venetoclax may not have been captured in the modelling, such as how it improves the productivity of working-age people with CLL. However, the committee agreed that such benefits were outside of the NICE reference case and that there were no relevant additional benefits that had not been captured in the QALY.</td>
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<tr>
<td>Are there specific groups of people for whom the technology is particularly cost effective?</td>
<td>There are no specific groups of people for whom the technology is particularly cost effective.</td>
<td></td>
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<tr>
<td>What are the key drivers of cost effectiveness?</td>
<td>The key drivers of cost-effectiveness are the source of best supportive care data, choice of distribution for the survival extrapolation and the choice of progression-free survival utility value.</td>
<td>4.14, 4.18, 4.25</td>
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<tr>
<td>Most likely cost-effectiveness estimate (given as an ICER)</td>
<td>The committee preferred the ERG's base-case assumptions. For both adults with a 17p deletion or TP53 mutation and adults without a 17p deletion or TP53 mutation, the ICERs were higher than the range usually considered a cost-effective use of NHS resources. However, as there are other plausible sources of best supportive care data available, the committee concluded that the ERG's base-case ICERs represented the lower end of the range of plausible ICERs, with the true ICERs potentially much higher.</td>
<td>4.23, 4.24, 4.25</td>
</tr>
</tbody>
</table>

### Additional factors taken into account

| Patient access schemes (PPRS) | - | - |
| End-of-life considerations | Based on the evidence available, the committee agreed that venetoclax met both the end-of-life criteria for both the populations with and without a 17p deletion or TP53 mutation. | 4.30 |
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.

Andrew Stevens
Chair, appraisal committee
February 2017

6 Appraisal committee members and NICE project team

Appraisal committee members

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

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

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

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

**Ross Dent**  
Technical lead

**Nicola Hay**  
Technical adviser

**Stephanie Yates**  
Project manager

ISBN: [to be added at publication]