

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal determination

**Venetoclax for treating chronic lymphocytic
leukaemia**

1 Recommendations

1.1 Venetoclax is recommended for use within the Cancer Drugs Fund, within its marketing authorisation, as an option for treating chronic lymphocytic leukaemia; that is in adults:

- with a 17p deletion or TP53 mutation and when a B-cell receptor pathway inhibitor is unsuitable, 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 and
- only if the conditions in the managed access agreement are followed.

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

2 The technology

<p>Description of the technology</p>	<p>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.</p>
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<p>Marketing authorisation</p>	<p>Venetoclax has a conditional marketing authorisation 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.’</p> <p>Before the marketing authorisation was granted, venetoclax was designated a promising innovative medicine and was available to patients in the NHS through the early access to medicines scheme.</p>
<p>Adverse reactions</p>	<p>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.</p>
<p>Recommended dose and schedule</p>	<p>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.</p>
<p>Price</p>	<p>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). The pricing arrangement considered during guidance development was that AbbVie had agreed a patient access scheme with the Department of Health. The managed access agreement agreed in August 2017 replaced this patient access scheme. As part of the managed access agreement, the company has a commercial access agreement with NHS England. This makes venetoclax available at a reduced cost. The financial terms of the agreement are commercial in confidence.</p>

3 Evidence

The appraisal committee (section 8) 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 them from living a normal life. The committee also heard that a proportion of patients spend a long time in the 'watch and wait' stage of the treatment pathway, anticipating relapse. This 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 adverse reactions, which are of particular concern for people diagnosed with CLL because many are older and may have comorbidities. 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:
 - for whom a B-cell receptor pathway inhibitor is unsuitable (population 1a) or
 - whose disease has progressed after a B-cell receptor pathway inhibitor (population 1b)
- without a 17p deletion or TP53 mutation and whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor (population 2).

4.4 The committee discussed population 1a (see section 4.3). It was aware that this group of people could previously have had either no therapy or chemo-immunotherapy. The committee noted that none of the venetoclax clinical trials defined unsuitability for a B-cell receptor pathway inhibitor; comments received from a professional group in response to consultation explained that this was because venetoclax and the B-cell receptor pathway inhibitors were being developed at the same time, so very few people had received the B-cell receptor pathway inhibitors when the venetoclax trials were designed. This meant that the company was unable to identify this group of patients in their clinical trials and did not present separate clinical effectiveness results for them. 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.

4.5 The committee discussed populations 1b and 2 (see section 4.3). 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.

- 4.6 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). Overall it concluded that it was not persuaded of the relevance of the population for whom a B-cell receptor pathway inhibitor is unsuitable to clinical practice in England.

Comparators

- 4.7 The company presented comparisons of venetoclax 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 active therapy (which may include rituximab monotherapy for symptom control). The committee concluded that best supportive care was a more appropriate comparator than no intervention (which 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

- 4.8 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 academic in confidence 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; after 12 months 88.1% of patients in the prior ibrutinib arm and 95.2% of patients in the prior idelalisib arm were alive.

4.9 The committee noted that the company's clinical effectiveness results 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 recruited only people with a 17p deletion or TP53 mutation, the analyses included both people for whom a B-cell receptor pathway inhibitor was unsuitable 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 separate populations in the marketing authorisation (see section 4.3).

4.10 The committee was concerned that the single-arm design of the trials made it difficult to assess the efficacy of venetoclax (that is, there was no comparator arm of patients having best supportive care). Moreover, the trials included relatively few patients and only 16 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). However, the committee recognised that the small number of patients was partly a result of the relative rarity of a 17p deletion or TP53 mutation. The committee was aware that in M14-032, neither the median progression-free survival nor median overall survival had been reached, and that because there was uncertainty associated

with the efficacy of venetoclax, the European Medicines Agency had granted the marketing authorisation for venetoclax conditional on the company submitting more mature data from M14-032, which is due to report in March 2018. The committee concluded that interpreting the results from the venetoclax trials was challenging without a direct comparator, and that this was compounded by the small patient numbers in the trials.

- 4.11 The committee noted comments, both from the clinical experts and from consultation, that venetoclax appears to be an effective therapy for people with few alternative treatment options. The comments highlighted that seeing tumour lysis syndrome in patients having venetoclax demonstrates its effectiveness, because this is a result of rapid tumour cell destruction. In addition, detectable disease was eradicated in a large proportion of patients in the trials, which is rarely seen in patients with CLL who have had many previous therapies. The committee concluded that there was a large degree of uncertainty in the clinical evidence, but acknowledged that venetoclax was an effective therapy compared with best supportive care.

Generalisability of the results

- 4.12 The committee was concerned about how generalisable the results of the venetoclax 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 patients in the trials had a mean age of 65 years and 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 reflected patients for whom venetoclax was likely to be an option in clinical practice in England, given that the mean age at diagnosis is 71 years and 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 the increased effect of advanced CLL on usual

daily activities. The committee further noted that the pooled health-related quality-of-life data collected in the venetoclax trials suggested that before disease progression, quality of life was higher than that for the age-matched general population. The committee was surprised that despite having several previous therapies, CLL appeared not to have a detrimental effect on the health-related quality of life of patients in the venetoclax trials. It concluded that this was further evidence that the venetoclax trial populations did not reflect people with advanced CLL seen in clinical practice in England. The committee noted consultation comments that based on the number of previous therapies, patients in the venetoclax trials reflected people for whom venetoclax would be an option in clinical practice in England. Moreover, it is common for clinical trials to select patients on the basis of younger age, good performance status and lack of significant comorbidities. The committee agreed that this was often the case, but in assessing clinical effectiveness this is normally mitigated by having a control arm with similar baseline characteristics, which is not the case for venetoclax. The committee concluded that patients 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

- 4.13 Venetoclax is associated with potentially serious adverse reactions such as tumour lysis syndrome, a consequence of rapid tumour cell death. The clinical expert explained that the 5-week dose escalation schedule helps to prevent tumour lysis syndrome and noted that there had been no clinical cases of tumour lysis syndrome reported in the venetoclax trials after this had been implemented. The committee acknowledged the risks associated with venetoclax treatment but concluded that it presented an acceptable safety profile.

Indirect comparison with best supportive care

- 4.14 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 progression-free and overall survival outcomes for venetoclax with best supportive care. The company used survival outcomes for best supportive care from the rituximab arm of the 116 randomised control trial, which compared idelalisib with rituximab for CLL.
- 4.15 To maximise the limited data from the venetoclax trials, the company pooled the venetoclax 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 lengths of time. However, the committee noted that pooling the data through a meta-analysis (the ERG's preferred method of estimating the hazard ratios for progression-free and overall survival associated with having a 17p deletion or TP53 mutation) 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.
- 4.16 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 had concerns about the comparison. Firstly, the rituximab arm of the 116 trial was composed entirely of patients eligible for idelalisib, whereas the marketing authorisation 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 noted comments during the first consultation suggesting that the company's comparison could be considered conservative. This is because best supportive care was approximated by patients 1 line of therapy earlier in the treatment pathway than patients eligible for venetoclax, so their survival was likely to be higher than if they had had a B-cell receptor pathway inhibitor. However, the committee noted that not only were the patients poorly matched, other evidence suggested that the venetoclax patients did not have more advanced disease. Health-related quality of life was higher than in the age-matched general population, the patients had not benefitted from a B-cell receptor pathway inhibitor and, despite venetoclax patients being 1 line of therapy later in the treatment pathway, median progression-free survival in M13-982 was 27.2 months compared with 19.4 months for idelalisib in the 116 trial. 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 in the company's pooled analysis was likely to be biased in favour of venetoclax.

Cost effectiveness

- 4.17 The committee discussed the company's economic model and modelling assumptions. The company modelled the populations as defined in the marketing authorisation. The committee was aware that this included people for whom a B-cell receptor pathway inhibitor is unsuitable and that the committee had not been persuaded of the relevance of this population to clinical practice in England (see section 4.6). The committee noted the model structure and concluded it was appropriate for its decision-making.

Venetoclax overall and progression-free survival extrapolations

4.18 The committee considered the company's parametric extrapolation of progression-free and overall survival 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, although 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 as well as a Weibull distribution. The committee was aware that extrapolations based on the Gompertz distribution resulted in lower progression-free and overall survival 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 progression-free survival rate from the Gompertz extrapolation (0%) was less clinically plausible than that from the Weibull extrapolation, in which some people were predicted to remain progression-free. The committee concluded that despite the uncertainty, the company's use of the Weibull distribution for the progression-free and overall survival extrapolations was justifiable.

Source of best supportive care data

4.19 The committee recalled that the company used 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. Instead, using the post-progression survival data from the idelalisib arm of the 116 trial would be more appropriate, because these patients all had disease progression after a B-cell receptor pathway inhibitor. 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 agreed that the idelalisib arm of the 116 trial after disease progression more closely matched the population who would be offered venetoclax and that it preferred the ERG's choice of best supportive care data.

- 4.20 In response to consultation, the company commented that the ERG's modelling of best supportive care based on post-progression in the idelalisib arm of the 116 trial was based on limited data, because few patients in the idelalisib arm had disease progression. The company also noted that the data could be confounded because some patients had a second dose of idelalisib after disease progression. The ERG acknowledged that only 17 patients had disease progression, but explained that the survival estimates were based on the difference between the overall survival and progression-free survival curves and therefore used data for all of the patients in the idelalisib arm. In addition, it commented that it was unclear which patients had a second dose of idelalisib and whether this would lead to better survival outcomes, given that their disease had already progressed. The company argued that the ERG's estimate of overall survival for best supportive care for patients with no 17p deletion or TP53 mutation of around 4 years was not consistent with the view of clinical experts that life expectancy for these patients is less than 24 months. The company provided alternative survival curves for best supportive care based on the assumption that mean overall survival for patients with no 17p deletion or TP53 mutation is 2 years. The resulting curve was adjusted using the ERG's hazard ratio to produce the corresponding survival curves for the population with a 17p deletion or TP53 mutation. The committee did not consider these

estimates to be an acceptable approach, because they were based only on assumptions and not on any epidemiological or clinical trial evidence.

4.21 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 (see section 4.16). The committee was also concerned that for the population without a 17p deletion or TP53 mutation, the ERG's modelling based on the idelalisib arm of the 116 trial suggested that post-progression survival was much longer than progression-free survival (4.02 years and 1.62 years respectively, see table 1), and it heard from clinical experts that 4 years of post-progression survival did not reflect clinical experience in England. However, the committee recalled that the patients in the venetoclax clinical trials do not reflect people who would be offered venetoclax in England either (see section 4.12). The committee accepted that although there were some limitations in how the ERG had modelled best supportive care, the ERG's approach was the most appropriate because patients in the idelalisib arm of the 116 trial with progressed disease were more similar to patients in the venetoclax trials than those in the rituximab arm of the 116 trial. The committee agreed to use the post-progression data from the idelalisib arm of the 116 trial to assess the comparative effectiveness of venetoclax and best supportive care, but did not give full weight to the ERG's estimates of post-progression survival, particularly for the population without a 17p deletion or TP53 mutation.

Table 1 Estimates of mean overall, progression-free and post-progression survival by deletion status from ERG and company models

	Overall survival	Progression-free survival	Post-progression survival
17p deletion or TP53 mutation			
Rituximab arm of 116 trial (company choice)	0.95 years	0.44 years	0.51 years
Idelalisib arm of 116 trial (ERG choice)	3.61 years	1.76 years	1.86 years
No 17p deletion or TP53 mutation			
Rituximab arm of 116 trial (company choice)	1.80 years	0.74 years	1.06 years
Idelalisib arm of 116 trial (ERG choice)	5.64 years	1.62 years	4.02 years

Utility values

4.22 The committee noted that in its original submission, the company used a utility 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. In response to consultation, the company commented that 0.71 was very close to the value for no response to treatment in the same publication (0.68), and was too low for the high proportion of venetoclax patients with a partial or complete response. It argued that the value of 0.80 from the Dretzke et al. publication was more appropriate, and highlighted that this was the value that had been accepted by the committee during the NICE technology appraisal of [idelalisib](#). The committee agreed that 0.71 was too low but noted that the value accepted by the committee during the idelalisib appraisal was in fact 0.748. The committee noted consultation comments highlighting that the company had originally used values from the venetoclax trials and so these were the most appropriate values. The committee agreed that although it would usually prefer to use these

values, it was not appropriate to do so here because patients in the venetoclax trials did not accurately reflect those seen in clinical practice in England (see section 4.12). 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 corrected utility value of 0.748 from the idelalisib appraisal was more appropriate.

Adverse event disutility and costs

4.23 The committee noted that the company had not included any 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

4.24 In response to the second consultation, the company revised its base case analyses (which used the rituximab arm of the 116 trial as the source of best supportive care data) by incorporating the committee's preferred utility and adverse event cost assumptions (see sections 4.22 and 4.23). For adults with a 17p deletion or TP53 mutation, whose disease has progressed after a B-cell receptor pathway inhibitor or for whom a B-cell receptor pathway inhibitor is unsuitable, the deterministic incremental cost-effectiveness ratio (ICER) for venetoclax compared with best supportive care was £39,940 per QALY gained. 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 ICER for venetoclax compared with best supportive care was £47,370 per QALY gained.

4.25 The committee considered the ERG's analyses using post-progression data after idelalisib in the 116 trial as the source of the best supportive

care data, which resulted in ICERs of £57,476 per QALY gained for adults with a 17p deletion or TP53 mutation and £77,779 per QALY gained for adults without a 17p deletion or TP53 mutation. The committee would have preferred to use probabilistic ICERs as the basis of its decision-making but neither the company nor the ERG had provided these for the analyses produced in response to consultation. The committee noted that although these ICERs reflected its other preferred modelling assumptions, they should be interpreted with caution, because of the uncertainty associated with the ERG's estimate of post-progression survival for the population without a 17p deletion or TP53 mutation (see section 4.21). On the other hand, the committee was aware that an ERG scenario analysis for the population with a 17p deletion or TP53 mutation using post-progression data after ibrutinib from the RESONATE trial as the source of best supportive care data increased the ICER to £61,120 per QALY gained. The committee considered that the population in the ERG's source of best supportive care data better matches the venetoclax trial populations (see section 4.21), so the ERG's model was appropriate for assessing the cost effectiveness of venetoclax compared with best supportive care. However, the committee acknowledged that overall survival with best supportive care could be lower than the ERG estimates, particularly for the population without a 17p deletion or TP53 mutation. It concluded that it was plausible that the ICERs for venetoclax could be around £50,000 and around £60,000 per QALY gained for the populations with and without a 17p deletion or TP53 mutation respectively, but agreed that uncertainty in the best supportive care overall survival estimate meant that all the ICERs were very uncertain.

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 it being an oral treatment. The committee noted that before the conditional

marketing authorisation was granted, venetoclax was available to patients in the NHS through the early access to medicines scheme. 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 although venetoclax is innovative, these 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. For the population with a 17p deletion or TP53 mutation, the mean overall survival was less than 24 months in both the company's and ERG's economic models. The committee concluded that the short life expectancy criterion was met in this population.
- 4.29 For the population without a 17p deletion or TP53 mutation, the company's model also suggested that mean overall survival was less than 24 months. However, in the ERG's model using the post-progression data from the idelalisib arm of the 116 trial, mean overall survival was just over 4 years (see table 1).
- 4.30 The committee recalled that, in response to the second consultation, both patient and professional organisations argued that in practice B-cell receptor pathway inhibitors are used late in the disease. They also reiterated that the estimate of 4 years' post-progression survival for people without a 17p deletion or TP53 mutation from the ERG's model is

not plausible highlighting data showing that in clinical practice in England life expectancy is less than 2 years for people stopping treatment with ibrutinib because of progressive disease. The committee accepted that the ERG's estimate did not reflect clinical experience in England, but also that the patients in the venetoclax trials did not reflect people who would be offered venetoclax in England (see section 4.12). The committee agreed that because the population in the ERG's source of best supportive care data matches the venetoclax trial populations (see section 4.21), the ERG's model was appropriate for assessing the relative benefit of venetoclax compared with best supportive care. However, it agreed that it could consider estimates of best supportive care informing the model separately from those informing the short life expectancy end-of-life criterion. The committee therefore concluded that the short life expectancy criterion was also met for the population without a 17p deletion or TP53 mutation.

- 4.31 The committee discussed whether venetoclax extended life by a mean of at least an additional 3 months compared with current NHS treatment. It noted that both the company's and ERG's modelling suggested that venetoclax was associated with a gain in mean overall survival of over 3 months, irrespective of the choice of best supportive care comparative data.
- 4.32 The committee concluded that venetoclax compared with best supportive care met both the end-of-life criteria for both populations (that is, with and without a 17p deletion or TP53 mutation). However, although the committee accepted that this meant that it was able to assign greater weight to the QALY benefits achieved from venetoclax, the most plausible ICERs were higher than the range usually considered to represent a cost-effective use of NHS resources for end-of-life treatments (see section 4.25). Furthermore, the committee was concerned about the substantial uncertainty around the ICER (see section 4.25) and agreed that the uncertainty must be taken into account in its decision-making. The

committee therefore did not recommend venetoclax for routine use within its marketing authorisation as a cost-effective use of NHS resources.

Cancer Drugs Fund considerations

- 4.33 Having concluded that venetoclax could not be recommended for routine use in either population, the committee then considered whether it could recommend venetoclax for treating CLL within the Cancer Drugs Fund. The committee discussed the new arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting the [addendum to the NICE process and methods guides](#).
- 4.34 Based on the cost-effectiveness evidence presented by the company and the ERG, the committee's preferred ICERs for venetoclax compared with best supportive care were based on the ERG's choice of best supportive care data. However, the committee was aware that there were some limitations to the ERG's approach. In particular, for the population without a 17p deletion or TP53 mutation, the ERG's model estimated much longer post-progression survival than progression-free survival (see section 4.21). In addition, the committee recalled comments from the clinical expert noting the shorter life expectancy of people having best supportive care in clinical practice in England. The committee considered that best supportive care overall survival could be below the ERG estimates, particularly for the population without a 17p deletion or TP53 mutation, and it concluded that the most plausible ICERs for venetoclax were around £50,000 and £60,000 per QALY gained for the populations with and without a 17p deletion or TP53 mutation respectively. However, the committee recognised that the relative clinical effectiveness of venetoclax was extremely uncertain and if it were closer to the company's estimates, then venetoclax would have the plausible potential to be cost effective (see section 4.24).
- 4.35 The committee noted that there are 2 main areas of uncertainty which make it difficult to assess the potential clinical benefits of venetoclax in

people for whom it would be an option in England. Firstly, the patients in the venetoclax trials had less advanced disease than would be expected in people having venetoclax in the NHS (see section 4.12). Secondly, the venetoclax clinical trials were all single arm, and there is no robust source of data available on survival after B-cell receptor pathway inhibitors. Evidence on venetoclax collected through the Cancer Drugs Fund would help to address the uncertainty about how effective it is in clinical practice in England. The committee also understood that because both ibrutinib and idelalisib in combination with rituximab had been available through the Cancer Drugs Fund, it would be possible to obtain post-progression survival outcomes after people stopped these treatments to inform a comparison with venetoclax. The committee agreed that this would provide a better estimate of the relative efficacy of venetoclax compared with best supportive care in the relevant patient populations than it had been presented with, although it noted that the comparison would still be naive and therefore subject to uncertainty.

4.36 The committee concluded that venetoclax met the criteria for inclusion in the Cancer Drugs Fund for both populations with and without the 17p deletion or TP53 mutation. It recommended venetoclax for use in the Cancer Drugs Funds, within its marketing authorisation, as an option for treating chronic lymphocytic leukaemia in adults:

- with a 17p deletion or TP53 mutation and a B-cell receptor pathway inhibitor is unsuitable, 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 and
- only if the conditions in the managed access agreements are followed.

Summary of appraisal committee's key conclusions

TAXXX	Appraisal title: Venetoclax for treating chronic lymphocytic leukaemia	Section
Key conclusion		
<p>Venetoclax is recommended for use within the Cancer Drugs Fund, within its marketing authorisation, as an option for treating chronic lymphocytic leukaemia (CLL) in adults:</p> <ul style="list-style-type: none"> • who have a 17p deletion or TP53 mutation, and a B-cell receptor pathway inhibitor is unsuitable or 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. <p>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.</p> <p>The committee agreed that there was substantial uncertainty related to the evidence base. The committee was concerned that the population in the venetoclax trials did not reflect patients seen in clinical practice in England and the single-arm design of the venetoclax trials meant that it was difficult to interpret the results in the absence of a direct comparator. However, the committee accepted comments from the clinical experts and those received in response to consultation that venetoclax was an effective therapy.</p>		<p>1.1, 4.6, 4.10– 4.12, 4.19– 4.21, 4.25, 4.32, 4.34, 4.35</p>

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, because 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 for whom venetoclax is likely to be used. The committee preferred this data source, but agreed that the comparison was still uncertain.

The committee agreed that both the populations with and without a 17p deletion or TP53 mutation met the end-of-life criteria. The most plausible ICERs continued to be higher than the range usually considered to represent a cost-effective use of NHS resources for end-of-life treatments. The committee concluded that venetoclax had the plausible potential to be cost effective if its relative effectiveness were closer to the company's estimate than the ERG's. Data collection in the Cancer Drugs Fund would resolve the uncertainty about the effectiveness of venetoclax when used in clinical practice in England, and data from when ibrutinib was in the Cancer Drugs Fund could be used to inform a better estimate of relative efficacy. The committee recommended venetoclax to be included in the Cancer Drugs Fund.

Current practice

<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The committee heard that current treatments are associated with adverse reactions, and that because many people diagnosed with CLL are older and may have comorbidities, many of these treatments are often not tolerated. The clinical expert stated that, once treatment options have been exhausted, prognosis is poor.</p>	<p>4.2</p>
<p>The technology</p>		
<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 accepted comments from the clinical expert and from consultation that venetoclax is an effective therapy compared with best supportive care.</p> <p>The committee noted that before the conditional marketing authorisation was granted, venetoclax was available to patients in the NHS through the early access to medicines scheme. The committee heard from the patient expert that they valued the fact that venetoclax was an oral treatment. The committee agreed that although venetoclax is innovative, there were no additional benefits that had not been captured in the QALY.</p>	<p>4.11, 4.26</p>

<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>The committee heard that venetoclax was likely to be used in clinical practice in patients:</p> <ul style="list-style-type: none"> • 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. 	<p>4.6</p>
<p>Adverse reactions</p>	<p>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.</p>	<p>2</p>
<p>Evidence for clinical effectiveness</p>		
<p>Availability, nature and quality of evidence</p>	<p>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 and difficult to assess in the absence of a direct comparison.</p> <p>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.</p>	<p>4.8, 4.9, 4.10</p>

<p>Relevance to general clinical practice in the NHS</p>	<p>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.</p> <p>The committee questioned whether the patients recruited to the venetoclax trials reflected 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.</p>	<p>4.12</p>
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<p>Uncertainties generated by the evidence</p>	<p>The committee agreed that the venetoclax trial results were uncertain.</p> <p>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.</p> <p>The committee agreed that the comparator population did not match that in the venetoclax trials because the population was 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 patients in the venetoclax trials. The committee agreed that the relative survival benefit of venetoclax compared with best supportive care was likely to be biased in favour of venetoclax.</p>	<p>4.8, 4.9, 4.10</p> <p>4.14</p> <p>4.16</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>There are no clinically relevant subgroups for which there is evidence of differential effectiveness.</p>	<p>–</p>

<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>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 had concerns about this comparison and concluded that the relative survival benefit of venetoclax compared with best supportive care was likely to be biased in favour of venetoclax.</p>	<p>4.16</p>
<p>Evidence for cost effectiveness</p>		
<p>Availability and nature of evidence</p>	<p>The company modelled the 2 populations as defined in the marketing authorisation. The committee noted that the model structure was appropriate for its decision-making.</p>	<p>4.17</p>

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The comparator population did not match the population in the venetoclax trials. This was because the comparator population was eligible for a B-cell receptor inhibitor, whereas to be offered venetoclax people must have disease progression after a B-cell receptor inhibitor.</p> <p>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 who would be offered venetoclax, the committee was concerned that the overall survival estimated by this approach did not reflect clinical experience in England.</p>	<p>4.19</p> <p>4.21</p>
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<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 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. In response to consultation, the company suggested that the value accepted by the committee for the idelalisib appraisal (NICE technology appraisal 359) was more appropriate than the ERG's preferred value from the literature. The committee agreed, and confirmed that the value that had been accepted was 0.748.</p> <p>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.</p>	<p>4.22, 4.26</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>There are no specific groups of people for whom the technology is particularly cost effective.</p>	<p>–</p>

<p>What are the key drivers of cost effectiveness?</p>	<p>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.</p>	<p>4.18, 4.21, 4.22</p>
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The committee preferred the ERG’s analyses using post-progression after idelalisib as the source of best supportive care data and a progression-free utility value of 0.748 aligned with NICE technology appraisal 359. For adults with a 17p deletion or TP53 mutation, the ICER was £57,476 per QALY gained and for adults without a 17p deletion or TP53 mutation, the ICER was £77,779 per QALY gained.</p> <p>However, the committee acknowledged that best supportive care overall survival could be lower than the ERG estimates, particularly for the population without a 17p deletion or TP53 mutation. It concluded that it was plausible that the ICERs for venetoclax could be around £50,000 and around £60,000 per QALY gained for the populations with and without a 17p deletion or TP53 mutation respectively, but agreed that uncertainty in the best supportive care overall survival estimate meant that the ICERs are very uncertain.</p>	<p>4.25</p>
<p>Additional factors taken into account</p>		

Patient access schemes (PPRS)	–	–
End-of-life considerations	Based on the evidence available, the committee agreed that venetoclax met the end-of-life criteria for both populations.	4.32
Equalities considerations and social value judgements	No equalities issues were identified during the appraisal.	–

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 according to the conditions in the managed access agreement. This means that, if a patient has chronic lymphocytic leukaemia and the doctor responsible for their care thinks that venetoclax 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 The Welsh Ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance where the drug or treatment, or other technology is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the Final

Appraisal Determination or agreement of a Managed Access Agreement by the NHS in Wales whichever is the latter.

- 5.3 Venetoclax has been recommended according to the conditions in the managed access agreement. As part of this, NHS England and AbbVie have a commercial access agreement that makes venetoclax 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 [NICE to add details at time of publication]

6 Recommendations for data collection

- 6.1 As a condition of the positive recommendation and the managed access agreement, data on time on treatment, overall survival and baseline characteristics of people taking venetoclax will be collected via the Systemic Anti-Cancer Therapy (SACT) dataset. The SACT dataset will also be used to collect time on treatment and overall survival data for people taking ibrutinib and idelalisib in combination with rituximab, to inform a comparison with best supportive care (see section 4.35).

7 Review of guidance

- 7.1 The guidance recommendation for this technology will be reviewed when the results of the data collection arrangement agreed by the company and NHS England as part of the managed access agreement are available (December 2020).

Andrew Stevens
Chair, appraisal committee
September 2017

8 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]**