NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Venetoclax for treating chronic lymphocytic leukaemia

1 Recommendations

1.1 Venetoclax monotherapy is recommended, within its marketing authorisation, for treating chronic lymphocytic leukaemia (CLL) 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.

It is recommended only if the company provides venetoclax according to the commercial arrangement (see section 2).

Why the committee made these recommendations

This appraisal reviews the additional evidence collected as part of the Cancer Drugs Fund managed access agreement for venetoclax for CLL.

People with CLL for whom venetoclax monotherapy would be an option would otherwise usually have best supportive care. This includes rituximab and high-dose methylprednisolone.

The new evidence is mainly data collected from the Systemic Anti-Cancer Therapy (SACT) database from people having treatment in the NHS, while venetoclax was available in the Cancer Drugs Fund in England. The benefit of venetoclax is uncertain because the original trials did not compare it with best supportive care, and no SACT data could be collected on best supportive care.

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Venetoclax meets NICE's criteria to be considered a life-extending treatment at the end of life. The cost-effectiveness estimates are around the range that NICE considers to be an acceptable use of NHS resources for end-of-life treatments. Venetoclax also fulfils an unmet need and is a valued treatment option. Therefore, it is recommended.

2 Information about venetoclax

Marketing authorisation indication

2.1 Venetoclax (Venclyxto, AbbVie) is indicated for 'the treatment of 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, or
- in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.'

Dosage in the marketing authorisation

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

Price

2.3 £4,789.47 per 112 tablet pack (100 mg) (excluding VAT; BNF online accessed February 2022). The average cost for year 1 is £58,752.23 and for year 2 onwards is £41,126.56.

The company has a commercial arrangement (simple discount patient access scheme). This makes venetoclax available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by AbbVie, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

This review looks at data collected after time in the Cancer Drugs Fund to address uncertainties identified during the original appraisal. Further information about the original appraisal can be found in the committee papers. As a condition of the Cancer Drugs Fund funding and the managed access agreement, data was collected on venetoclax for people with chronic lymphocytic leukaemia (CLL) in the NHS through the Cancer Drugs Fund using the Systemic Anti-Cancer Therapy (SACT) dataset.

Clinical need and treatment pathway

Chronic lymphocytic leukaemia has a substantial effect on quality of life

3.1 CLL is the most common form of leukaemia and is associated with fatigue and recurrent infections. The patient experts explained that the disease is commonly relapsing-remitting and so patients are often thinking about the next treatment and the challenges this will bring. They described the significant physical, mental and financial effect on people with CLL and their families. The committee concluded that CLL has a substantial effect on quality of life.

Venetoclax monotherapy is an important option for some people with relapsed chronic lymphocytic leukaemia

3.2 Since the original appraisal of venetoclax for CLL, NICE has recommended venetoclax with obinutuzumab (see NICE's technology appraisal guidance on venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia) and with rituximab (see NICE's technology appraisal guidance on venetoclax with rituximab for previously treated chronic lymphocytic leukaemia). The B-cell receptor pathway inhibitor acalabrutinib has also been recommended for untreated CLL

(see NICE's technology appraisal guidance on acalabrutinib for treating chronic lymphocytic leukaemia). The clinical experts explained that most people with CLL have acalabrutinib or ibrutinib as first-line treatment and then venetoclax with rituximab as second-line, or venetoclax with obinutuzumab as first-line treatment and acalabrutinib or ibrutinib as second-line. Chemo-immunotherapy is rarely used. Despite the changes to the treatment pathway since the original appraisal, clinical and patient experts considered that there was still an unmet need for people with relapsed CLL who have tried other treatments or who cannot have rituximab. The committee concluded that venetoclax monotherapy would be an important option for these people.

The population should be considered as a whole

3.3 The clinical experts explained that splitting the population by 17p deletion or TP53 mutation status is less relevant now than when venetoclax was originally appraised. This is because the split was largely based on the different effect of chemo-immunotherapy depending on whether a 17p deletion or TP53 mutation was present, and now chemo-immunotherapy is rarely used. The committee noted that the company's model results were presented separately for each population but that it would prefer to make the same recommendation for both groups. The committee noted there was not a large difference in the cost effectiveness between the groups. It concluded that the population should be considered as a whole.

Best supportive care is an appropriate comparator

3.4 In the original appraisal, the comparator was best supportive care, which the company defined as rituximab and high-dose methylprednisolone. In the original appraisal, the committee concluded that best supportive care was an appropriate comparator. In line with NICE's guide to the process of technology appraisal, the original scope was not changed for this Cancer Drugs Fund review. The clinical experts explained that best supportive care would include regular monitoring and transfusions and could include chemo-immunotherapy in some cases. The committee

concluded that best supportive care was the appropriate comparator for this Cancer Drugs Fund review.

Clinical effectiveness

It is acceptable to use SACT data to represent venetoclax efficacy, but the costs of rituximab should be added to the venetoclax arm

3.5 The company used data from the SACT dataset, which was collected while venetoclax was available through the Cancer Drugs Fund, for the clinical efficacy evidence for venetoclax. The company preferred to use this data, rather than data from the 3 venetoclax trials it had used in the original appraisal, because it considered the SACT Cancer Drugs Fund data was more generalisable to clinical practice in the NHS in England. The SACT Cancer Drugs Fund dataset comprised 406 people with CLL who had venetoclax. The data from the SACT Cancer Drugs Fund cohort showed that the median overall survival for the overall cohort was 43.1 months. For the subgroup with a 17p deletion or TP53 mutation, median overall survival was 33 months, and for the subgroup without a 17p deletion or TP53 mutation, median overall survival was not reached. The ERG highlighted that people in the SACT Cancer Drugs Fund cohort could switch from venetoclax monotherapy to venetoclax with rituximab and that 80 out of the 406 people had had rituximab on or after starting venetoclax. It explained that the benefit people got from adding rituximab was unknown, and that the company had not accounted for the costs of rituximab. The ERG also stated that in clinical practice, people for whom venetoclax monotherapy was suitable may have had previously had venetoclax with rituximab or obinutuzumab. The ERG was concerned that the efficacy of venetoclax as retreatment may be lower than in the SACT Cancer Drugs Fund cohort, who were unlikely to have already had venetoclax. The clinical experts stated that evidence from the MURANO trial suggested that venetoclax was effective as a retreatment after previous venetoclax with rituximab. The committee acknowledged that there were limitations in using the SACT Cancer Drugs Fund data, but it

agreed that this data was the best available data to represent venetoclax efficacy and was acceptable to use in this appraisal. The committee also concluded that because some people in the SACT Cancer Drugs Fund cohort had rituximab on or after starting venetoclax, these costs should be accounted for in the modelling.

Despite significant issues, the rituximab arm of trial 116 is the best available source to model best supportive care

3.6 Because there were no trials that directly compared venetoclax with best supportive care, in the original appraisal the company used data from the placebo with rituximab arm of trial 116 to model best supportive care. Trial 116 was a randomised controlled trial which compared idelalisib plus rituximab with placebo plus rituximab. Further data on best supportive care had been expected from the Cancer Drugs Fund, but this could not be collected. Therefore, the company retained its approach of using the placebo plus rituximab arm from trial 116 to model best supportive care in the current Cancer Drugs Fund review. The company considered that the people in this dataset better aligned with the SACT Cancer Drugs Fund data than they had with the original venetoclax trials, because they had a more similar stage of disease. In the original appraisal, the committee had accepted using post-progression survival from the idelalisib with rituximab arm of trial 116 to model overall survival for best supportive care. However, the company stated that this was now considered less appropriate than the placebo plus rituximab arm because of the high post-progression survival of 4 years with idelalisib, which did not reflect clinical practice in the UK. The ERG also acknowledged that the idelalisib plus rituximab arm had limitations and was associated with implausible extrapolations for the subgroup with a 17p deletion or TP53 mutation. However, the ERG did not consider that the rituximab arm from trial 116 was a suitable comparator. This was because it was at an earlier point in the treatment pathway than venetoclax would be used, and people in trial 116 had other treatment options, which may have improved their survival after the study. There were also differences in the eligibility

criteria between trial 116 and the SACT Cancer Drugs Fund. These included differences in previous treatments, whether people who had had a stem cell or solid organ transplant were included, and whether the time between previous treatment and progression was specified. The ERG identified some alternative potential sources of data for best supportive care, from studies by Aarup et al. (2020) and Rigolin et al. (2021). These gave comparable estimates of median overall survival to the company model. However, the company noted that neither of these studies included anyonefrom the UK. The committee noted that in the study by Aarup, 60% of people had further treatment, some of whom had venetoclax. People in the study by Rigolin et al. also had further treatments, although further details of these were not reported. For these reasons, the committee agreed that these 2 studies did not represent best supportive care. The clinical experts stated that there was a lack of evidence on best supportive care and agreed that trial 116 was a better source of comparator data than the 2 studies identified by the ERG. The clinical experts considered that the choice of arm from trial 116 may have a limited effect on overall survival for best supportive care because of treatment crossover within the trial. The committee concluded that, despite significant issues, the rituximab arm of trial 116 was the best evidence it had been presented with to model best supportive care.

The ERG's statistical comparison of venetoclax with best supportive care is not appropriate for decision making

3.7 The company did not present a statistical comparison of venetoclax with best supportive care, with matching for baseline characteristics or eligibility criteria. Instead, the relative benefit of venetoclax compared with best supportive care was based solely on survival models fitted to the clinical data. The ERG had concerns over this and considered that a statistical comparison would have value. It compared data from the SACT Cancer Drugs Fund cohort and additional data from people who had venetoclax as part of the Early Access to Medicines Scheme, with combined data from Rigolin et al. (2021) and Aarup et al. (2020) (see

section 3.6). From this analysis, the ERG calculated a hazard ratio of 0.57 for overall survival between venetoclax and best supportive care. It applied this hazard ratio to the company's survival extrapolations of best supportive care (see section 3.10) to derive survival extrapolations for venetoclax. The committee did not consider this analysis to be informative because of its concerns that the Rigolin et al. and Aarup et al. studies did not represent best supportive care (see section 3.6). It concluded that the ERG's statistical comparison of venetoclax with best supportive care was not appropriate for decision making.

Cost effectiveness

The company's model structure is acceptable for decision making

3.8 The company presented a partitioned survival model to assess the cost effectiveness of venetoclax. The model included 3 health states: progression-free disease, progressed disease and death. The committee noted that the model structure had not changed since the original appraisal, in which it had been considered acceptable. The committee concluded that the model structure was acceptable for decision making.

The company's modelling of venetoclax overall survival is acceptable for decision making

3.9 To extrapolate beyond the observed time period of data collected for venetoclax, the company fitted parametric survival models to data recreated from the SACT report. It selected a Weibull model for extrapolating overall survival. The ERG highlighted that the observed data showed the hazard rate increasing towards the end of follow up for the subgroup with a 17p deletion or TP53 mutation, and that the same would likely be seen in the longer term for the subgroup without a 17p deletion or TP53 mutation. In contrast, the Weibull model selected by the company had a continuously decreasing hazard rate. The ERG explained that this led to high estimates of post-progression survival for venetoclax in the company's model. It identified a paper by Eyre et al. (2019), which

reported the post-progression survival times of 22 people from the UK after having venetoclax. The ERG fitted parametric curves to the data from Eyre et al. to compare survival times with those from the company's model. Post-progression survival for venetoclax in the company's model was much higher than in the ERG's estimates based on Eyre et al. The ERG presented a scenario analysis in which it reduced the post-progression survival for venetoclax to be more in line with the estimates derived from Eyre et al. In response to technical engagement, the company updated its modelling, which decreased post-progression survival times for venetoclax by increasing progression-free survival (see section 3.11). However, the company continued using the Weibull model to extrapolate overall survival for venetoclax. The ERG considered that a model that captured an increasing hazard rate would have been preferable. The company highlighted that the increasing hazard rate seen by the ERG could have been because of small numbers of people remaining alive beyond 2 years. The company also noted that other more flexible models that it fitted during technical engagement were unable to capture the increasing hazard rate. This suggested that the increasing hazard rate could be an artefact of the small patient numbers remaining at risk. The clinical experts considered that the SACT Cancer Drugs Fund data was a more robust source of evidence for venetoclax than Eyre et al. The committee noted that the ERG's analysis involved pooling transition probabilities from venetoclax and best supportive care, which it considered added further uncertainty because of the uncertainty with the evidence for best supportive care (see section 3.6). The committee concluded that the company's modelling of venetoclax overall survival was acceptable for decision making.

The company's more consistent updated survival modelling approach is acceptable

3.10 For venetoclax, the company fitted independent parametric models to data from the SACT report for people with CLL with and without a 17p deletion or TP53 mutation. For best supportive care, it fitted 1 dependent

survival model to data from the rituximab arm of trial 116 simultaneously for both populations. For the subgroup without a 17p deletion or TP53 mutation, it applied a hazard ratio (0.585 for progression-free survival and 0.543 for overall survival) to the model for the subgroup without a 17p deletion or TP53 mutation. The company derived these hazard ratios from pooled data from the venetoclax trials. The ERG did not consider it appropriate to use a hazard ratio derived from venetoclax data to apply to the best supportive care model, or to model the 2 arms differently. In response to technical engagement, the company updated its modelling of venetoclax to fit a single dependent model, including a hazard ratio to model the relationship between the 2 populations. It also explored further extrapolation models beyond the Weibull model it had originally selected. It updated its base-case model to include a dependent Weibull model for overall survival, and a dependent normal spline 2-knot model for time on treatment. The committee concluded that the company's more consistent updated survival modelling approach was acceptable.

It is plausible that progression-free survival is equivalent to time on treatment

3.11 Progression-free survival data was unavailable from the SACT Cancer Drugs Fund dataset, so the company used time-on-treatment data to approximate progression-free survival for venetoclax. It also noted that using time-on-treatment data for venetoclax was inconsistent with the way the company had modelled best supportive care, where time-on-treatment data had not been used. In response to technical engagement, the company estimated the relationship between time on treatment and progression-free survival from 2 of the venetoclax trials. It calculated 2 separate hazard ratios for people with CLL with and without a 17p deletion or TP53 mutation. It then applied these hazard ratios to its base case model, to estimate progression-free survival curves for venetoclax, separate to the time-on-treatment curves. This reduced post-progression survival for venetoclax compared with the company's original model. The ERG considered that the company's updated modelling of venetoclax was

still inconsistent with the modelling of best supportive care because progression-free survival and time on treatment were not modelled separately for best supportive care. The company highlighted that best supportive care was assumed to be rituximab (see section 3.6), which has a fixed duration of treatment, so it is more logical not to include time on treatment for the best supportive care arm. The clinical experts explained that few people having venetoclax stop treatment before progression. So, in practice there is likely to be little difference between time on treatment and progression-free survival, although there is uncertainty because some people may progress early but keep having treatment. The committee concluded that it was plausible that progression-free survival was equivalent to time on treatment for people having venetoclax.

End of life

Venetoclax meets the criteria to be considered a life-extending treatment at the end of life

3.12 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. In the original appraisal, the data showed that venetoclax compared with best supportive care met both the end-of-life criteria for both populations. The committee did not hear any evidence to change this conclusion. Therefore, it concluded that venetoclax met the end-of-life criteria and could be considered a life-extending treatment at the end of life.

Cost-effectiveness results

Venetoclax is recommended for routine use

3.13 The company's base-case deterministic incremental cost-effectiveness ratios (ICERs) for both the subgroups with and without a 17p deletion or TP53 mutation were around £50,000 per QALY gained. These results included the patient access scheme discount for venetoclax and the confidential commercial discounts for other treatments. The ERG

corrected an error in the company's model. It presented a scenario analysis in which the costs of rituximab were included in the venetoclax arm, which the committee had agreed was appropriate (see section 3.5). It presented a further scenario analysis in which progression-free survival was equal to time on treatment for venetoclax, which the committee had agreed was appropriate (see section 3.11). These both increased the ICERs, and the ICER for the subgroup without a 17p deletion or TP53 mutation was above £50,000 per QALY gained. The committee recalled that it would prefer to consider the population as a whole, rather than split by 17p deletion or TP53 mutation status (see section 3.3). It considered that the ICERs for the whole population would likely be between those for the subgroups with and without a 17p deletion or TP53 mutation. The committee acknowledged that venetoclax monotherapy fulfilled an unmet need and was aware of its value to patients as another treatment option for CLL (see section 3.2). Because of changes in the treatment pathway since the original appraisal, it was also likely that a relatively small number of people would have venetoclax monotherapy in future. So the consequences of decision error were low. The committee therefore recommended venetoclax for routine use.

Other factors

There are no equality issues, and all relevant benefits are captured in the QALY

3.14 A stakeholder highlighted that CLL is a disease that mainly affects older people. The committee agreed that its recommendations did not have a different impact on people protected by the equality legislation than on the wider population. It concluded that there were no equality issues, and all relevant benefits of the technology were captured in the QALY calculations.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has chronic lymphocytic leukaemia and the doctor

responsible for their care thinks that venetoclax is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Richard Nicholas
Chair, appraisal committee
March 2022

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.

Kirsty Pitt

Technical lead

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Technical adviser

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