NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Venetoclax with a hypomethylating agent for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable

The Department of Health and Social Care 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 experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: September 2021

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 document.
- Subject to any appeal by consultees, the final appraisal document 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: 25 October 2021

Second appraisal committee meeting: 9 November 2021

Details of membership of the appraisal committee are given in section 5

1 Recommendations

1.1 The committee recognised that venetoclax plus azacitidine is a promising new treatment, but was not persuaded that there is sufficient evidence of clinical and cost effectiveness to recommend it for routine commissioning for untreated acute myeloid leukaemia in adults when intensive chemotherapy is unsuitable.

1.2 Given the uncertainties, the committee considered that venetoclax plus azacitidine may be suitable for use in the Cancer Drugs Fund. Therefore the company is invited to submit a proposal for including venetoclax plus azacitidine in the Cancer Drugs Fund for untreated acute myeloid leukaemia in adults when intensive chemotherapy is unsuitable.

1.3 The Cancer Drugs Fund proposal should:

- detail any commercial access arrangements
- show plausible potential for cost effectiveness
- explain how data collection will address the main clinical uncertainties described in section 3
- state the likelihood that additional research will reduce uncertainty enough to support positive guidance in the future
- state how data will be collected and what data is currently available
- state when the results will be available.

If appropriate data is already being collected, summarise the study protocol.

Why the committee made these recommendations

When intensive chemotherapy is unsuitable, active treatment for untreated acute myeloid leukaemia is usually azacitidine or low dose cytarabine. The clinical trial evidence shows that people having venetoclax plus azacitidine live longer than people having azacitidine or low dose cytarabine alone.

Venetoclax with azacitidine meets NICE's criteria for a life-extending treatment at the end of life. The cost-effectiveness results are uncertain because it is not clear whether people who have venetoclax plus azacitidine are cured if their disease remains in remission for a certain amount of time, or what this time period might be. Also, the dose of venetoclax used to work out the cost-effectiveness estimates was different to that used in clinical practice, which makes the results more uncertain. Some of the likely cost-effectiveness estimates are higher than is normally considered a cost-effective use of NHS resources. Therefore, venetoclax plus azacitidine is not recommended for routine use in the NHS. However, it could be suitable for use in the Cancer Drugs Fund, if the company puts forward a proposal.

2 Information about venetoclax

Marketing authorisation indication

2.1 Venetoclax (Venclyxto, AbbVie) in combination with a hypomethylating agent is indicated for 'the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy'.

Dosage in the marketing authorisation

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

Price

2.3 The cost of venetoclax is £299.34 for 7 x 100 mg tablets (excluding VAT; BNF online accessed September 2021). The cost of azacitidine is £220 per 100 mg vial (excluding VAT; BNF online accessed September 2021). Costs may vary in different settings because of negotiated procurement discounts.

The company has a commercial arrangement. This makes venetoclax available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. 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.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

- The general population mortality adjustment should be removed from the transition to the progression/relapse health state in the model (issue 2, see ERG report section 4.2.6)
- The company's updated approach to modelling time to treatment discontinuation is acceptable (issue 3, see ERG report section 4.2.6)
- It is acceptable in this case for adverse event data in the model to be sourced from a separate study to the VIALE trials, because it is unlikely to have a big impact on the cost-effectiveness results (issue 4, see ERG report section 4.2.7)
- It is acceptable in this case for treatment-independent utility values in the model to be derived from pooled data from both VIALE-A and VIALE-C, because it is unlikely to have a big impact on the cost-effectiveness results (issue 4, see ERG report section 4.2.7)
- 7 days' wastage for venetoclax should be included in the model to account for tablets that are prescribed but not used because of treatment discontinuation or death during a cycle (issue 6, see ERG report section 4.2.8).

The committee recognised that there were remaining areas of uncertainty associated with the analyses presented and took these into account in its decision making. It discussed issues 1, 5 and an additional issue identified at technical engagement, issue 7, which were outstanding after the technical engagement stage.

New treatment option

People with acute myeloid leukaemia for whom intensive chemotherapy is unsuitable would welcome a new treatment option

3.1 Intensive chemotherapy is unsuitable for about 40% of people with untreated acute myeloid leukaemia. This may be because of fitness status, age or presence of comorbidities. The patient expert explained that patients in this group feel that treatment options for them are very limited. They value increased survival as much as increased quality of life, and the possibility of long-term remission with venetoclax plus azacitidine is appealing. Clinical experts also stated that there is a significant unmet need for new treatments for this population because outcomes are poor with currently available treatments. Venetoclax is an oral treatment that can be taken at home, so the time patients need to be in hospital might be significantly reduced. Patients would also appreciate being able to manage side effects at home when possible. The committee concluded that people with acute myeloid leukaemia for whom intensive chemotherapy is unsuitable would welcome a new treatment option.

Comparators

Splitting the trial population by blast cell count is necessary to compare venetoclax plus azacitidine with the relevant comparators but increases uncertainty

3.2 The evidence for venetoclax came from a randomised controlled trial, VIALE-A (n=431), which compared venetoclax plus azacitidine with azacitidine alone in people with untreated acute myeloid leukaemia who could not have intensive chemotherapy because of age or comorbidities. The clinical experts considered that the population in the trial would be generalisable to people who would be eligible for venetoclax plus azacitidine in England. In clinical practice in England, when intensive chemotherapy is unsuitable, acute myeloid leukaemia is treated with either azacitidine or low dose cytarabine. In the NHS in England, the

hypomethylating agent used is azacitidine. NICE's technology appraisal of azacitidine (TA218) recommends azacitidine only for acute myeloid leukaemia with 20% to 30% blasts. In practice, this means that low dose cytarabine is used for acute myeloid leukaemia with over 30% blasts. Therefore, the company did a post hoc subgroup analysis to split the trial population by blast count. It used the data from the subgroup with 20% to 30% blasts to compare venetoclax plus azacitidine with azacitidine alone. Another randomised controlled trial, VIALE-C (n=211), compared venetoclax and low dose cytarabine with low dose cytarabine alone in the same overall population as VIALE-A. To compare venetoclax plus azacitidine with low dose cytarabine in the group with over 30% blasts, the company used the over 30% blasts subgroup data on venetoclax plus azacitidine from VIALE-A, and data on low dose cytarabine from a subgroup with over 30% blasts from VIALE-C. The committee concluded that it was necessary to use the subgroup data to compare venetoclax plus azacitidine with the relevant comparators in clinical practice in England, but that the subgroup analysis increased uncertainty in the results.

Clinical efficacy

Venetoclax plus azacitidine increases overall survival compared with azacitidine or low dose cytarabine alone

3.3 The post hoc subgroup analysis splitting the trial population by blast count showed that venetoclax plus azacitidine increased overall survival compared with azacitidine alone in the subgroup with 20% to 30% blasts, but the increase was not statistically significant. The company noted that the VIALE trials were not powered to identify clinical benefit in these subgroups. The company considers the exact results to be academic in confidence, so they cannot be reported here. The post hoc analysis comparing venetoclax plus azacitidine (from VIALE-A) with low dose cytarabine (from VIALE-C) in the group with over 30% blasts showed that venetoclax plus azacitidine increased overall survival compared with low

dose cytarabine, and that this increase was statistically significant. The company considers the exact results to be academic in confidence so they cannot be reported here. The company also did a network meta-analysis and propensity score matching to compare results across the 2 trials in the group with over 30% blasts, and noted that the results were similar to those of the unadjusted comparison. The committee concluded that venetoclax plus azacitidine increases overall survival compared with azacitidine or low dose cytarabine alone.

Economic model

The company's economic model included a cure health state

3.4 The company presented a cohort Markov state transition economic model to assess the cost effectiveness of venetoclax plus azacitidine. The model included 5 health states: remission, non-remission, cure, progressive disease/relapse and death. In the company's model, patients having venetoclax who were alive after 2 years of being in the remission health state moved into the cure state. In the cure health state, patients were assumed to have the same utility value as that of the general population. Patients having azacitidine alone could not transition to the cure state.

The evidence is too uncertain to include a cure health state in the model

3.5 The company stated that the VIALE-A results showed that complete remission rates with venetoclax plus azacitidine were similar to those seen in patients over 60 receiving intensive chemotherapy, and that rates of sustained deep remission were higher with venetoclax plus azacitidine than with azacitidine alone. It argued that it was therefore plausible to assume that patients having venetoclax plus azacitidine could be considered cured. It cited clinical advice that the rate of relapse after 2 years in remission is low and commented that there was a plateau in the Kaplan–Meier curve at 2 years. The ERG noted that there was a lack of long-term data to validate a cure assumption because the maximum follow up in VIALE-A was 2.56 years. It highlighted that, historically, non-

intensive treatments such as azacitidine and low dose cytarabine have not been considered curative in this population, and that the Kaplan–Meier curve was based on very few patients by 2 years. The ERG presented several scenarios in which it removed the cure state in the model and investigated alternative extrapolations for the time-from-remission-to-relapse curves for venetoclax plus azacitidine. The ERG pointed out that using these parametric curves, some patients in the model would never relapse. That is, a proportion would achieve a cure. At technical engagement, a professional organisation highlighted a small study by Chyn Chua et al. comparing stopping venetoclax treatment in remission with continuing it until relapse. The results suggested that venetoclax could be stopped after 2 years in remission without a negative impact on outcomes. However, the committee noted that in this study, a number of relapses occurred after 2 years. The clinical experts stated that it was plausible that there could be a proportion of patients who are cured after having venetoclax, but that it was difficult to specify a time frame and there was a lack of evidence to inform this. They stated that many people would return to the same quality of life after treatment as could be expected in the general population, but that some would not. They also explained that around 25% to 30% of people in this population have acute myeloid leukaemia with an NPM1 mutation, and that these patients may be more likely to be cured. The company highlighted that a cure assumption had been included in NICE's technology appraisal of gilteritinib for treating relapsed or refractory acute myeloid leukaemia (TA642). However, the committee noted that this appraisal was in a different population and that although the committee had accepted a cure assumption applied to all patients alive at between 2 and 3 years in the gilteritinib model, a substantial proportion of people in the trial had received a stem cell transplant. The committee agreed that any cure state in the model should have applied to both arms. It did not consider it plausible that patients in the cure state would experience the same quality of life as the general population. The committee agreed that the cure state

should be removed, but it could not choose between the ERG's scenarios with alternative time-to-relapse curves without any data on the proportions of people surviving to different time points. The committee noted that cure fractions estimated from a mixture cure model may have been helpful to validate the proportion of patients remaining in the remission health state over time. The committee concluded that the evidence was too uncertain to include a cure health state in the model and that it was unclear which time-to-relapse curve should be used.

The company's updated assumptions about the proportions of people having subsequent gilteritinib are acceptable

3.6 In the company's original model, 3% of people in the venetoclax plus azacitidine arm had gilteritinib after venetoclax plus azacitidine, and all others having subsequent treatment had hydroxycarbamide. The ERG suggested this proportion should be higher, based on clinical advice. At technical engagement, clinical experts and professional groups agreed that around 10% of people may have FLT3-mutation-positive disease and be eligible for gilteritinib after venetoclax plus azacitidine, azacitidine alone or low dose cytarabine. The company cited clinical advice that suggested more people who had venetoclax with azacitidine would be able to have subsequent treatment with gilteritinib than people who had azacitidine alone, because it was more likely their disease would go into complete remission. The company updated its base case to include 5% of people having gilteritinib after venetoclax plus azacitidine and 3% having gilteritinib after azacitidine or low dose cytarabine. It also presented a scenario analysis showing that increasing the proportions to 15% after venetoclax plus azacitidine and 10% after azacitidine or low dose cytarabine had a small impact on the cost-effectiveness results. The ERG's clinical expert considered that the company's updated base-case assumptions were plausible. The committee agreed that the company's updated base-case assumptions were acceptable to use in the model.

The dose intensity of venetoclax used in clinical practice is likely to be between 12.5% and 25% of the full licensed dose

3.7 The dose of venetoclax in the summary of product characteristics in VIALE-A and in the company's model was 400 mg daily, after treatment initiation. The company applied a dose intensity of 50% to venetoclax in its model, based on clinical advice that the amount of venetoclax received by patients in the VIALE-A trial was higher than would be expected in clinical practice in England. At technical engagement, clinical experts stated that in clinical practice in England, almost all patients with acute myeloid leukaemia would have concomitant treatment with azoles such as posaconazole as antifungal prophylaxis. Azoles are strong CYP3A inhibitors, which affects the metabolism of venetoclax and increases its plasma level. Therefore, in line with the summary of product characteristics advice on managing potential venetoclax interactions with CYP3A inhibitors, the dose of venetoclax used in clinical practice would be much lower than in the trial, usually 100 mg a day rather than 400 mg. The clinical experts also stated that they would often only give venetoclax for 14 days from the second cycle onwards, rather than 28 days, to limit toxicity. The clinical experts cited some pharmacokinetic data that showed that the plasma level of venetoclax was maintained when a lower dose was given with azoles, but the committee understood that this effect may vary between individuals. The company stated that, in a limited analysis, it had found no statistically significant difference in efficacy for people in the VIALE trials who had a lower dose of venetoclax with azoles, compared with the higher dose. The ERG presented scenarios that reduced the dose intensity of venetoclax in the model to 25% and 12.5%. The committee agreed that the dose intensity in clinical practice in England would likely be 25% of the full licensed dose for the first cycle, and 12.5% from cycle 2 onwards. It noted that it would have found it helpful to see the results from the pharmacokinetic studies. It concluded that the dose of venetoclax in the model should be lower to reflect clinical practice, which was likely to be between the 2 ERG scenarios.

End of life

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

3.8 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. Median overall survival in the VIALE trials for people having azacitidine in the 20% to 30% blast count group and low dose cytarabine in the over 30% blast count was under 24 months. The company considers the exact figures to be academic in confidence and so they cannot be reported here. Mean undiscounted life years in the model were 1.83 years for the azacitidine (20% to 30% blast count) arm and 0.84 years for the low dose cytarabine (over 30% blast count) arm. The committee agreed that the short life expectancy criterion was met. The median increases in overall survival from the trials for venetoclax plus azacitidine compared with azacitidine alone in the 20% to 30% blast count group and compared with low dose cytarabine in the over 30% blast count group were over 3 months. The company considers the exact figures to be academic in confidence so they cannot be reported here. The mean incremental undiscounted life years in the model were 1.33 to 2.40 years across all ERG scenarios for venetoclax plus azacitidine compared with azacitidine alone (20% to 30% blast count) and 1.33 to 2.71 years across all ERG scenarios for venetoclax plus azacitidine compared with low dose cytarabine (over 30% blast count). The committee agreed that the extension to life criterion was met. It therefore concluded that venetoclax plus azacitidine met the criteria to be considered a life-extending treatment at the end of life.

Cost-effectiveness results

The upper end of the plausible ICER range is above £50,000 per QALY gained

3.9 The company's original base-case incremental cost-effectiveness ratio (ICER) for venetoclax plus azacitidine compared with azacitidine in the 20% to 30% blasts population was £38,866 per quality-adjusted life year (QALY) gained. All analyses included the patient access scheme for venetoclax, but not the patient access scheme for gilteritinib, which was included as a subsequent treatment in the model. The results including the discount for gilteritinib are commercial in confidence and cannot be reported here. The company's original base-case ICER for venetoclax plus azacitidine compared with low dose cytarabine in the over 30% blasts population was £39,449 per QALY gained. In response to technical engagement, the company:

- corrected errors in the model relating to time on treatment and the maximum trial follow up included
- removed the general population mortality adjustment from the transition to the progressed disease/relapse state
- updated the modelling of time to treatment discontinuation
- updated the proportions of people having subsequent treatment with gilteritinib (see section 3.6), and
- applied 7 days' drug wastage for venetoclax.

The ERG corrected an error in the cost of subsequent treatment. These changes and corrections resulted in an updated company base-case ICER of £24,596 per QALY gained for venetoclax plus azacitidine compared with azacitidine alone in the 20% to 30% blasts population, and £41,361 per QALY gained compared with low dose cytarabine in the over 30% blasts population. In its exploratory analyses, the ERG preferred to use alternative costs for adverse events in the model, to account for long-stay admissions. It also removed the cure assumption, which significantly

increased the ICERs. The ERG presented the same analyses with both a 25% and 12.5% dose intensity (see section 3.7), which decreased the ICERs. The committee agreed that the dose intensity should be between 12.5% and 25% and that any of the ERG's scenarios in which the cure assumption was removed and alternative time-to-release curves were used were plausible (see section 3.5). This led to plausible ICER ranges of £48,976 to £64,586 per QALY gained for venetoclax plus azacitidine compared with azacitidine, and £50,871 to £77,032 per QALY gained for venetoclax plus azacitidine compared with low dose cytarabine. When the ERG included the confidential discount for gilteritinib subsequent treatment in its analyses, the ICERs decreased slightly. Because of the confidentiality of this discount, the exact ICERs cannot be reported here. The committee concluded that the upper end of the plausible ICER range was over £50,000 per QALY gained.

Venetoclax with azacitidine is not recommended for routine use in the NHS

3.10 Because some of the plausible ICERs were above the range that NICE normally considers to be a cost-effective use of NHS resources for a life-extending treatment at the end of life, the committee concluded it could not recommend venetoclax plus azacitidine for routine use for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable.

Cancer Drugs Fund

Venetoclax with azacitidine may be suitable for use in the Cancer Drugs Fund

3.11 Having concluded that venetoclax could not be recommended for routine use, the committee then considered if it could be recommended for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS

England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum).

- The company had not expressed an interest in venetoclax being considered for funding through the Cancer Drugs Fund.
- The key uncertainty was if and when a cure could be assumed for all patients on venetoclax plus azacitidine who were still in remission after a given timepoint.
- The committee's preferred ICER ranges spanned £50,000 per QALY gained, so there was plausible potential for venetoclax plus azacitidine to be cost effective.
- The committee considered that longer-term data from the clinical trials had the potential to address the uncertainty around the cure assumption, and longer follow up would increase the numbers at risk in the Kaplan–Meier curves, reducing uncertainty in the extrapolations for the time-to-relapse curves.

The committee concluded that venetoclax plus azacitidine could meet the criteria to be considered for inclusion in the Cancer Drugs Fund. It agreed to invite the company to submit a proposal for including venetoclax plus azacitidine in the Cancer Drugs Fund as an option for people with untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable.

Other factors

There are no equality issues relevant to the recommendations

3.12 A committee member highlighted that venetoclax could provide an effective treatment option for older people who have not benefitted from other recent advances in treatment, and that anyone who cannot easily travel to a major hospital may particularly benefit from being able to take venetoclax at home. The committee considered these potential issues but noted that recommendations would apply to all patients, regardless of age

or location. It concluded that no equality issues relevant to the recommendations had been identified.

The benefits of venetoclax are captured in the cost-effectiveness analysis

3.13 The company, professional organisations and clinical experts considered that venetoclax was innovative because it was a targeted therapy, was different to currently available therapies, led to increased overall survival and rates of complete and deep remissions, and decreased the need for blood transfusions. The committee agreed that these were important benefits of venetoclax, but concluded that it had not been presented with evidence of any additional benefits that were not captured in the QALY calculation.

4 Proposed date for review of guidance

4.1 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.

Stephen O'Brien
Chair, appraisal committee
October 2021

5 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

Alex Filby
Technical adviser

Louise Jafferally
Project manager

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