NICE National Institute for Health and Care Excellence

NICE guidance

Venetoclax with azacitidine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable

Technology appraisal guidance

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Your responsibility

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

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

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

Contents

1 Recommendations

1.1 Venetoclax with azacitidine is recommended, within its marketing authorisation, as an option for untreated acute myeloid leukaemia in adults when intensive chemotherapy is unsuitable. It is recommended only if the company provides venetoclax according to the commercial arrangement.

Why the committee made these recommendations

When intensive chemotherapy is unsuitable, 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 how many people who have venetoclax plus azacitidine might be considered cured. However, the likely cost-effectiveness estimates are within the range that NICE normally considers an acceptable use of NHS resources. Therefore, venetoclax plus azacitidine is recommended.

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 for venetoclax.

Price

2.3 The cost of venetoclax is £299.34 for 7×100 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). The company has a commercial arrangement. 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.

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).
- Seven 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 with currently available treatments are poor. 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 the NHS in England, when intensive chemotherapy is unsuitable, acute myeloid leukaemia is treated with either azacitidine or low dose cytarabine. NICE's technology appraisal guidance on azacitidine recommends azacitidine only for acute myeloid leukaemia with 20% to 30% bone marrow blasts (from here, 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-level state transition 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 original model, patients having venetoclax who were alive after 2 years of being in the remission health state moved into the cure state. Patients having azacitidine alone could not transition to the cure state.

The evidence for including a cure state in the model is uncertain, but it is plausible that some people may be cured

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 there was an established relationship between complete remission and long-term survival, and that it was therefore plausible to assume that some 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 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. At technical engagement, a professional organisation highlighted a small study by Chyn Chua et al. comparing stopping venetoclax treatment while in remission, with continuing it until relapse. It considered that 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. At consultation, the authors of the study commented that most of the late relapses were associated with new molecular

or cytogenetic abnormalities, suggesting they were not relapses of the original disease. The company highlighted that a cure assumption had been included in NICE's technology appraisal guidance on gilteritinib for treating relapsed or refractory acute myeloid leukaemia. 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 also noted that the cure assumption in the gilteritinib model applied to both the gilteritinib and salvage chemotherapy arms, whereas in the venetoclax model it only applied to the venetoclax arm. The committee agreed that any cure state in the venetoclax model should have been applied to both arms. However, the ERG presented scenario analyses applying the cure state to the azacitidine and low dose cytarabine arms, and this only had a small impact on the cost-effectiveness results. At consultation, the company updated its base-case model so that people moved into the cure state after 3 years of being in remission, instead of 2 years. It also presented scenario analyses in which only a proportion of people in remission transitioned to the cure state. The rest remained in the remission state with a continuing disease-related risk of relapse and death. The ERG presented further scenario analyses with alternative proportions and noted that the cost-effectiveness results were not sensitive to the different proportions explored in these scenarios. The clinical experts estimated that 10% to 20% of people having venetoclax plus azacitidine may reach 3 years without a relapse and that 80% to 90% of these people would then never have a relapse. They explained that around 30% of people in this population have acute myeloid leukaemia with an NPM1, IDH1 or IDH2 mutation, and that these patients may be more likely to be cured. At the first committee meeting, the committee noted that cure fractions estimated from a mixture cure model may have been helpful to provide some basis for validating the proportion of patients remaining in the remission health state over time. At consultation, the company presented the proportion of people remaining in remission at various time points, based on removing the cure state and applying mixture cure models to separate transitions (from remission to relapse and from remission to death) to validate the proportion of the overall cohort who were in remission at different time points. The committee noted that it would have preferred to see the cure fraction reported from a mixture cure model fitted to the overall population. The committee concluded that the evidence for including a cure state in the model was uncertain, but that it was plausible that some people could be

considered cured.

Using the remission state utility value in the cure state does not affect the cost-effectiveness results

3.6 In the cure health state, patients were assumed to have the same utility value as that of the general population. The clinical experts stated that most people would return to the same level of quality of life after treatment as could be expected in the general population, but that a small number would not. The committee did not consider it plausible that patients in the cure state would experience the same level of quality of life as the general population. However, at consultation, the company stated that because of the age of patients in the model at the point of cure, the age-adjusted general population utility was always lower than the remission health state utility. Therefore, using the remission utility value in the cure state, capped by general population utility, had no effect on the cost-effectiveness results. The committee accepted that using the remission state utility value in the cure state did not affect the cost-effectiveness results.

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

3.7 In the company's original model, 3% of people in the venetoclax plus azacitidine arm had gilteritinib after venetoclax plus azacitidine, and all others who had 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 company's updated modelling of dose intensity reflects clinical practice

3.8 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 affect the metabolism of venetoclax and increase 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 company highlighted the summary of product characteristics for venetoclax, which notes that in most cases, this should be considered once the person's disease is in remission. The committee agreed that the dose intensity of venetoclax in the NHS in England would likely be 25% of the full licensed dose for the first cycle, and 12.5% from cycle 2 onwards. In response to consultation, the company updated its model to use a dose intensity for venetoclax of 25% for the first cycle and 12.5% from cycle 2 onwards. It presented a pharmacokinetic study that showed that a 100 mg dose of venetoclax given with a strong CYP3A inhibitor led to drug exposure between that of a 400 mg dose and the safe maximum dose of 1,200 mg per day. The company also presented a post hoc analysis of VIALE-A data showing that complete remission rates were similar when an adjusted dose was given with a CYP3A inhibitor, compared with the licensed dose and no CYP3A inhibitor. The committee concluded that the company's updated modelling was appropriate and reflected clinical practice.

End of life

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

3.9 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 group was under 24 months. The company considers the exact figures to be academic in confidence and so they cannot be reported here. The 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 increases in median 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 over 3 months across all scenarios for venetoclax plus azacitidine compared with azacitidine alone (20% to 30% blast count) and 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

All the plausible ICERs presented are below £50,000 per QALY gained

3.10 All analyses included the patient access scheme for venetoclax. After technical engagement, the company's base-case incremental cost-effectiveness ratio (ICER) was £24,824 per quality-adjusted life year (QALY) gained for venetoclax plus azacitidine compared with azacitidine alone in the 20% to 30% blasts population, and £41,481 per QALY gained compared with low dose cytarabine in the over 30% blasts population. This included a cure point at 2 years. 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 corrected an error in the cost of subsequent treatment. After consultation, the company presented a revised base case, which included:

- the ERG's correction and alternative costs for adverse events
- a cure state at 3 years instead of 2 (see section 3.5)
- the dose intensity of venetoclax that reflects clinical practice (see section 3.8).

This resulted in an updated base-case ICER of £26,760 per QALY gained for venetoclax plus azacitidine compared with azacitidine alone in the 20% to 30% blasts population, and £38,900 per QALY gained compared with low dose cytarabine in the over 30% blasts population. The company and ERG presented scenario analyses in which only a proportion of people who were in remission at 3 years were assumed to be cured. 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 noted that the ICER remained below £50,000 per QALY gained when only 10% or less of the patients in remission at 3 years were considered cured. The committee understood that this proportion was considerably lower than the proportion that the clinical experts had considered plausible (80% to 90%). The committee concluded that all the plausible ICERs presented were below £50,000 per QALY gained.

Venetoclax with azacitidine is recommended for routine use in the NHS

3.11 Because all of the plausible ICERs were within 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 recommended venetoclax plus azacitidine as an option for untreated acute myeloid leukaemia in adults when intensive chemotherapy is unsuitable. This includes those in the 20% to 30% blast group and the over 30% blast group.

Equality and innovation

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 the recommendation 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 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 acute myeloid leukaemia, intensive chemotherapy is unsuitable and the doctor responsible for their care thinks that venetoclax plus azacitidine is the right treatment, it should be available for use, in line with NICE's recommendations.

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.

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Accreditation