National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Venetoclax with a hypomethylating agent or low dose cytarabine for untreated acute myeloid leukaemia when intensive chemotherapy is unsuitable [ID1564]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	AbbVie Ltd	Yes	No action required
	Royal College of Physicians (RCP)	Yes	No action required
Wording	AbbVie Ltd	Yes	No action required
	Royal College of Physicians (RCP)	Yes	No action required
Timing Issues	AbbVie Ltd	There are limited treatments for AML in people for whom intensive chemotherapy is not suitable, and the prognosis in this population is typically poor. As such, there is a substantial unmet need for novel treatment options.	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Royal College of Physicians (RCP)	Current standard of care low dose cytarabine (LDAC) and azacitidine (AZA) lack efficacy such that patients have a very limited life expectancy- there is an urgent unmet clinical need.	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AbbVie Ltd	AbbVie would like to further emphasise the variety of symptoms experienced by patients with AML, including fever, weight loss, and bruising. In addition, patients are frequently hospitalised for the purposes of treatment, transfusions, and to monitor side effects. Taken together these factors contribute to a substantial quality of life impact of AML on patients. AbbVie suggest clarifying in the last paragraph that there are 'limited' alternative treatment options.	Comment noted. The background section is intended to give a brief summary of the disease area and the wording is in line with other recent scopes for acute myeloid leukaemia. No action required Comment noted. No action required.
	Royal College of Physicians (RCP)	Important to highlight that such patients who are treated with LDAC/AZA have a limited life expectancy (approx. 6 months) and have a very high dependency on healthcare support- for management of infections and blood transfusions.	Comment noted. The background section is intended to give a brief summary of the disease area and the wording is in line with other recent scopes for acute myeloid leukaemia.

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The technology/ intervention	AbbVie Ltd	AbbVie suggest clarifying that the clinical trials Venetoclax is being studied in combination with low dose cytarabine or azacytidine are in comparison to low dose cytarabine or azacitidine. AbbVie suggest including the full wording for all CLL indications for which venetoclax is currently approved: • Venetoclax in combination with rituximab is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy. • Venetoclax in combination with obinutuzumab for the treatment of adult patients with previously untreated CLL • Venetoclax monotherapy 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.	Comment noted. CLL is not within the remit of this appraisal. No action required.
	Royal College of Physicians (RCP)	Yes- worth noting that Venetoclax has FDA approval “In combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.”Nov 2018.	Comment noted. The appraisal would be conducted within the UK NHS setting. No action required.
Population	AbbVie Ltd	The population is defined appropriately.	Comment noted. No action required.

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	Royal College of Physicians (RCP)	Yes	No action required
Comparators	AbbVie Ltd	AbbVie agree that low dose cytarabine and azacitidine represent the standard of care comparators for venetoclax with a hypomethylating agent or low dose cytarabine.	Comment noted. No action required
	Royal College of Physicians (RCP)	YES- a proportion of frail elderly AML patients are not considered fit for LDAC/AZA(and get best supportive care)- in part due to poor performance status and low response rates- that assessment could change with the availability of more effective therapy.	Comment noted. Best supportive care added to the list of comparators.
Outcomes	AbbVie Ltd	The listed outcomes are suitable, but should also include 'blood transfusion independence', as this is a relevant outcome in this population. This is in alignment with prior azacitidine appraisals (TA218; TA399)	Comment noted. The list of outcomes in the scope is not intended to be exhaustive, the appraisal committee can consider other outcomes if appropriate. These are also likely to be indirectly captured in the cost-effectiveness analysis. Blood transfusion independence added to the list of outcomes.

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	Royal College of Physicians (RCP)	Additionally hospital days and transfusion independence if available may be informative	Comment noted. The list of outcomes in the scope is not intended to be exhaustive, the appraisal committee can consider other outcomes if appropriate. These are also likely to be indirectly captured in the cost-effectiveness analysis. Blood transfusion independence added to the list of outcomes.
Economic analysis	AbbVie Ltd	No comments.	No action required
	Royal College of Physicians (RCP)	As outlined above life expectancy for this population is short- the time horizon required is therefore frequently short to enable appropriate clinical and economic evaluation	Comment noted. No action required.
Equality and Diversity	AbbVie Ltd	No comments.	No action required
	Royal College of Physicians (RCP)	No	No action required
	AbbVie Ltd	No comments.	No action required

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Other considerations	Royal College of Physicians (RCP)	N/A	No action required
Innovation	AbbVie Ltd	Venetoclax is a highly innovative medicine; there has been no significant innovation for AML patients that are unsuitable for intensive chemotherapy since 2011. As such, venetoclax offers a step change in the treatment of this condition.	Comment noted. The extent to which venetoclax is an innovative technology will be considered by the appraisal committee in its decision making. No action required.
	Royal College of Physicians (RCP)	The FDA approval was based upon Venetoclax studied in two open-label non-randomized trials in patients with newly-diagnosed AML who were ≥75 years of age, or had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2-3, severe cardiac or pulmonary comorbidity, moderate hepatic impairment, or CLcr <45 mL/min or other comorbidity. Efficacy was established based on the rate of complete remission (CR) and the duration of CR. 145 patients were treated in combination with hypomethylating agents (AZA and Decitabine) with a 67% response rate (CR/CRi) and median OS of 17.5 months. 82 patients were treated in combination with LDAC with a response rate of 54% (CR/CRi) and median OS of 10.1months. The results of the completed randomised phase 3 studies VIALE-C (LDAC+/- VEN) and VIALE-A (AZA +/- VEN) have both been reported/published this year. VIALE-C confirmed the high response rates with the addition of Venetoclax but did not meet the predetermined primary endpoint in terms of improved overall survival. VIALE-A demonstrated at a median follow-up of 20.5 months, the median overall survival was 14.7 months in the azacitidine–venetoclax group	Comment noted. The extent to which venetoclax is an innovative technology will be considered by the appraisal committee in its decision making. No action required.

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		and 9.6 months in the control group (hazard ratio for death, 0.66; 95% confidence interval, 0.52 to 0.85; P<0.001).a composite complete remission (complete remission or complete remission with incomplete hematologic recovery) (66.4% vs. 28.3%; P<0.001) NEJM 2020. The results have been widely accepted as VEN-AZA being the new standard of care for this patient group.	
Questions for consultation	AbbVie Ltd	The anticipated position of venetoclax with a hypomethylating agent or low dose cytarabine is as frontline therapy for patients with AML for whom intensive chemotherapy is unsuitable. AbbVie does not anticipate any barriers to adoption of this technology into practice.	Comment noted. No action required.
	Royal College of Physicians (RCP)	N/A	No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope