Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of azacitidine within its marketing authorisation for treating acute myeloid leukaemia with more than 30% bone marrow blasts and when haematopoietic stem cell transplantation is not suitable.

Background

Acute myeloid leukaemia (AML) is a bone marrow cancer characterised by the overproduction of early immature myeloid cells (blasts). Myeloid neoplasms with more than 20% blasts in the peripheral blood or bone marrow are considered AML. In most types of AML, the leukaemia cells are immature white blood cells. In other less common types, too many immature platelets or immature red blood cells are made. Anaemia, bleeding problems and serious infections are the common symptoms in AML.

The incidence of AML in England is about 2500 cases per year. Around three quarters of all cases occur in those over 60 years. It is slightly more common in men than in women.

AML is classified according to the World Health Organisation (WHO) classification which takes in to account morphology, cytochemistry, immunophenotype, cytogenetics and clinical information and categorises AML into several clinically relevant disease entities. Cytogenetics is the single most important prognostic factor and it classifies patients into 'favourable, intermediate or adverse risk' groups based on the presence or absence of specific chromosomal patterns. Poor prognostic factors, including intermediate and adverse risk cytogenetics, are more common in older people, making treatment particularly challenging.

AML typically develops rapidly and worsens in a few weeks unless treated. People for whom intensive chemotherapy is suitable are treated with cytotoxic agents such as anthracyclines in combination with cytarabine. People in intermediate and poor-risk groups with good performance status may also receive allogeneic stem cells transplantation. Those who cannot tolerate or do not wish to receive intensive chemotherapy are given non-intensive (palliative) chemotherapy with agents such as low dose cytarabine, decitabine, hydroxycarbamide, mercaptopurine or etoposide. NICE technology appraisal guidance No. 218 recommends azacitidine for adults with acute myeloid leukaemia with 20–30% blasts and multilineage dysplasia, according to the

WHO classification and who cannot have haematopoietic stem cell transplantation. Other aspects of care include blood product replacement for anaemia and thrombocytopenia, antibiotics and antifungals for infections and allopurinol to reduce uric acid levels.

The technology

Azacitidine (Vidaza, Celgene) is an analogue of nucleotide cytidine that reduces DNA methylation by inhibition of DNA methyltransferase. Azacitidine is administered subcutaneously.

Azacitidine does not currently have a marketing authorisation in the UK for acute myeloid leukaemia with more than 30% bone marrow blasts and when haematopoietic stem cell transplantation is not suitable. It has been studied in clinical trials in patients of age 65 years or more with acute myeloid leukaemia with bone marrow blasts more than 30%, who are not eligible for haematopoietic stem cell transplant compared with intensive chemotherapy with anthracycline in combination with cytarabine, low dose cytarabine, or best supportive care.

Azacitidine has a UK marketing authorisation for acute myeloid leukaemia with 20-30 % blasts and multi-lineage dysplasia, according to the World Health Organisation classification.

Intervention(s)	Azacitidine
Population(s)	Adults with acute myeloid leukaemia with bone marrow blasts more than 30% who are not eligible for haematopoietic stem cell transplantation
Comparators	• Intensive chemotherapy with anthracycline in combination with cytarabine • Non-intensive chemotherapy with - low dose cytarabine - decitabine • best supportive care which may include low dose chemotherapy (such as hydroxycarbamide, mercaptopurine, etoposide), antibiotics, antifungals, blood product replacement and allopurinol

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates, including haematologic response and improvement • blood-transfusion independence • infections • adverse effects of treatment • health-related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Technology Appraisal No. 218, March 2011, 'Azacitidine for the treatment of myelodysplastic syndrome, chronic myelomonocytic leukaemia and acute myeloid leukaemia'. Transferred to the 'static guidance list' April 2014 Technology Appraisal No. 270, December 2012, Decitabine for the treatment of acute myeloid leukaemia (terminated appraisal). Related Cancer Service Guidance: Guidance on Cancer Services, CSGHO, October 2003, 'Improving outcomes in haematological cancers'

	Related NICE Pathways: NICE Pathway: Blood and bone marrow cancers, Pathway last updated: December 2014, http://pathways.nice.org.uk/pathways/blood-and-bone-marrowcancers
Related National Policy	Blood and marrow transplantation services (all ages), Chapter 29, Manual for Prescribed Specialised Services 2013/14 http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domains 1 and 2 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

Questions for consultation

Is the trial population, that is, people of age 65 years or more with acute myeloid leukaemia with bone marrow blasts more than 30% who are not eligible for haematopoietic stem cell transplant, expected to be the subject of the marketing authorisation?

Have all relevant comparators for azacitidine been included in the scope? Which treatments are considered to be established clinical practice in the NHS for acute myeloid leukaemia with more than 30% bone marrow blasts?

- Is decitabine an appropriate comparator for this appraisal? Is it used in routine clinical practice for treating acute myeloid leukaemia with bone marrow blasts more than 30% who are not eligible for haematopoietic stem cell transplantation in England?
- Do patients who are not eligible for haematopoietic stem cell transplantation receive intensive chemotherapy in routine clinical practice in England?
- Is best supportive care an appropriate comparator? How should it be defined?

Are there any subgroups of people in whom azacitidine is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider azacitidine will fit into the existing NICE pathway, Blood and bone marrow cancers?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which azacitidine will licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider azacitidine to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of azacitidine can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction)