NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Oral azacitidine for maintenance treatment of acute myeloid leukaemia after induction therapy

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of oral azacitidine within its marketing authorisation as maintenance treatment for adults with acute myeloid leukaemia after induction therapy.

Background

Acute myeloid leukaemia is a cancer of the blood and bone marrow. It is characterised by the overproduction of early immature myeloid cells (blasts). Acute myeloid leukaemia is classified into different types. In most types of acute myeloid leukaemia, the leukaemia cells are immature white blood cells. In other less common types, too many immature platelets or immature red blood cells form leukaemia cells. Anaemia, bleeding problems and serious infections are common symptoms of acute myeloid leukaemia.

The incidence of acute myeloid leukaemia has increased by 7% in the UK over the last decade.[1] There are around 3,200 new diagnoses of acute myeloid leukaemia in the UK per year.[1] The incidence rate increases with age with the highest rates being in the 85 to 89 age group.[1] There are around 2,600 acute myeloid leukaemia deaths registered in the UK per year.[1]

The aim of treatment for acute myeloid leukaemia is to cure it. For people who are fit enough to have intensive treatment, induction chemotherapy is initially given to achieve a remission. Around 66% of people who have standard induction chemotherapy have disease remission.[2] After remission, further cycles of chemotherapy are sometimes given to reduce the risk of the leukaemia recurring (consolidation therapy). Maintenance therapy is long term treatment to prevent the cancer returning when it is in remission or to prolong remission. People with good general health may have a stem cell transplant to replace damaged blood cells with healthy ones, however some people may not be eligible because of underlying health conditions that could complicate the transplant.

For people with untreated disease:

- NICE technology appraisal 552 recommends liposomal cytarabine-daunorubicin as a treatment option.
- NICE technology appraisal 545 recommends gemtuzumab ozogamicin with daunorubicin and cytarabine as a treatment option for people with de novo CD33-positive acute myeloid leukaemia.
- NICE technology appraisal 523 recommends midostaurin as a treatment option for newly diagnosed acute FLT3-mutation positive myeloid leukaemia

with standard daunorubicin and cytarabine as induction therapy, with high-dose cytarabine as consolidation therapy, and alone after complete response as maintenance therapy.

- NICE technology appraisal 399 does not recommend subcutaneous azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts in people 65 years or older who are not eligible for haematopoietic stem cell transplant.

- NICE technology appraisal 218 recommends subcutaneous azacitidine as a treatment option for adults who are not eligible for haematopoietic stem cell transplant and have acute myeloid leukaemia with 20-30% blasts and multilineage dysplasia according to the World Health Organization classification.

The only treatment option currently recommended by NICE as maintenance therapy for acute myeloid leukaemia is midostaurin.

The technology

Azacitidine (Onureg, Celgene, a BMS company) is an analogue of the nucleoside cytidine that reduces DNA methylation by inhibition of DNA methyltransferase. Oral azacitidine has a distinct pharmacokinetic profile from injectable azacitidine. This formulation of azacitidine is administered orally.

Oral azacitidine does not currently have a marketing authorisation in the UK for maintenance treatment of acute myeloid leukaemia after induction therapy. In June 2021, the European Medicines Agency authorised oral azacitidine for use 'as maintenance therapy in adult patients with acute myeloid leukaemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, hematopoietic stem cell transplantation (HSCT)'. Oral azacitidine has been studied in a clinical trial in addition to best supportive care compared with placebo and best supportive care in adults aged 55 or older who had newly diagnosed acute myeloid leukaemia.

Azacitidine (for injection) has a marketing authorisation for treating adults 'who are not eligible for haematopoietic stem cell transplantation (HSCT) with:

• intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS),

• chronic myelomonocytic leukaemia (CMML) with 10-29% marrow blasts without myeloproliferative disorder,

• acute myeloid leukaemia (AML) with 20-30% blasts and multi-lineage dysplasia, according to World Health Organisation (WHO) classification,

• AML with > 30% marrow blasts according to the WHO classification'.

Intervention(s)	Oral azacitidine

Population(s)	Adults with acute myeloid leukaemia who have complete disease remission, or complete remission with incomplete blood count recovery, following induction therapy who are not eligible for haematopoietic stem cell transplant
Comparators	• Midostaurin • Established clinical management without oral azacitidine
Outcomes	The outcome measures to be considered include: • overall survival • relapse free survival • 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 commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.
Other considerations	The availability and cost of biosimilar and generic products should be taken into account. 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: 'Liposomal cytarabine and daunorubicin for untreated acute myeloid leukaemia' (2018) NICE technology appraisal 552. 'Gemtuzumab ozogamicin for untreated acute myeloid leukaemia' (2018) NICE technology appraisal guidance 545. 'Midostaurin for untreated acute myeloid leukaemia' (2018) NICE technology appraisal guidance 523.

	'Azacitidine for treating acute myeloid leukaemia with more than 30% bone marrow blasts' (2016) NICE technology appraisal guidance 399. 'Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia' (2011) NICE technology appraisal guidance 218. Review date April 2014. Appraisals in development (including suspended appraisals) 'Histamine dihydrochloride with interleukin-2 for maintenance treatment of acute myeloid leukaemia' (suspended) NICE technology appraisals guidance [ID1627]. Related Guidelines: 'Haematological cancers: improving outcomes' (2016). NICE Guideline 47. Related Quality Standards: 'Haematological cancers' (2017). NICE quality standard 150. Related NICE Pathways: Blood and bone marrow cancers (2021) NICE pathway.
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019): Chapter 29 Department of Health and Social Care (2016) NHS Outcomes Framework 2016-2017: Domains 3, 4 and 5.

Questions for consultation

What technologies are currently used for the maintenance treatment of acute myeloid leukaemia after induction therapy?

How should established clinical management without oral azacitidine be defined?

Are the outcomes listed appropriate?

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

Where do you consider oral azacitidine will fit into the existing NICE pathway for 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 oral azacitidine will be 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 oral 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 oral 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.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

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).

References

1 Cancer Research UK (2016) Acute myeloid leukaemia (AML) statistics. Accessed June 2021.

2 American Cancer Society (2018) Treatment Response Rates for Acute Myeloid Leukemia (AML). Accessed June 2021.