NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Gilteritinib for treating relapsed or refractory acute myeloid leukaemia

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of gilteritinib within its marketing authorisation for treating relapsed or refractory positive acute myeloid leukaemia.

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.

FMS-like tyrosine kinase-3 (FLT3) is a receptor tyrosine kinase. FLT3 is a cell-surface receptor involved in the proliferation, or increase, in the number of certain blood cells. Mutations in the FLT3 gene occurs in around 30% of patients with AML. FLT3 mutations can be either internal tandem duplications (FLT3-ITD mutations) or point mutations of the tyrosine kinase domain (FLT3-TKD mutations). Around 60% of patients with mutations in the FLT3 gene will relapse within the first 2 years of induction therapy.

The incidence of acute myeloid leukaemia has increased by 8% in the UK over the last decade. There were 2,662 new diagnoses of acute myeloid leukaemia in England in 2016.[1] The incidence rate increases with age with the highest rates being in the 85 to 89 age group. There were 2,168 deaths registered in England in 2016.[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. After remission, further cycles of chemotherapy are given to reduce the risk of the leukaemia recurring (consolidation therapy). The treatment of relapsed or refractory AML depends upon several factors such as age, general health, type of leukaemia cells and duration of remission (in case of relapsed AML). For people with good general health, the treatment typically includes chemotherapy and allogeneic haematopoietic stem cell transplant. The aim of chemotherapy is to reduce the leukemic burden before haematopoietic stem cell transplant. Allogeneic haematopoietic stem cell transplant means that stem cells were donated by someone else, usually a sibling whose tissue type closely matches that of the patient.

People with relapsed or refractory AML are offered salvage chemotherapy regimens containing high-dose of cytarabine such as fludarabine, cytarabine, granulocyte-colony stimulating factor (G-CSF) with idarubicin (FLAG-Ida). People who cannot tolerate or do not wish to receive high-dose cytarabine are offered intermediate dose cytarabine regimen (IDAC). People with relapsed and refractory AML also receive supportive care, which includes, blood product replacement, antibiotics, and antifungals. People who cannot have chemotherapy and stem cells transplant, need intermittent hydroxycarbamide to keep peripheral leukaemia cell count under control.

The technology

Gilteritinib (Xospata, Astellas Pharma Inc) is a tyrosine kinase-3 (FLT3) and AXL inhibitor. It is administered orally. AXL is a receptor tyrosine kinase (RTK). AXL is a cell-surface receptor involved in the proliferation and survival of cells. It also mediates migration and invasiveness of cancer cells.

Gilteritinib does not currently have a marketing authorisation in the UK for acute myeloid leukaemia. It has been studied alone in a clinical trial in adults with relapsed or refractory FLT3-mutation positive acute myeloid leukaemia. The clinical trial compares gilteritinib to salvage chemotherapy (low dose cytarabine [LoDAC]; azacitidine; mitoxantrone, etoposide, cytarabine (MEC); or FLAG-Ida.

Intervention(s)	Gilteritinib
Population(s)	Adults with relapsed or refractory FLT3-mutation positive acute myeloid leukaemia
Comparators	Established clinical management without gilteritinib, for example: • Intermediate dose cytarabine (IDAC) • fludarabine, cytarabine, granulocyte-colony stimulating factor (G-CSF) with idarubicin (FLAG-Ida) • Best supportive care • Quizartinib subject to ongoing NICE appraisal (ID1325) • Hydroxycarbamide (for people who cannot have chemotherapy or stem cell transplant)

Outcomes	The outcome measures to be considered include: • overall survival • event-free survival • disease-free survival • response rates, including remission • stem cell transplant • 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 economic modelling should include the costs associated with diagnostic testing for FLT3 mutation in people with acute myeloid leukaemia who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals
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** **Terminated appraisals** 'Decitabine for the treatment of acute myeloid leukaemia' (terminated appraisal) (2012) NICE Technology Appraisal 270. **Appraisals in development (including suspended appraisals)** 'Quizartinib for treating relapsed or refractory acute myeloid leukaemia' [ID1325]. Expected publication date

	TBC 'Vosaroxin for treating relapsed or refractory acute myeloid leukaemia' NICE technology appraisals guidance [ID746]. Suspended 2016. **Related guidelines** 'Haematological cancers: improving outcomes' (2016). NICE Guideline 47. Review date to be confirmed. **Related NICE Pathways**: Blood and bone marrow cancers (2018) NICE pathway http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp
Related National Policy	Department of Health Cancer research and treatment Department of Health (2016) NHS Outcomes Framework 2016 to 2017: Domains 3, 4 and 5. Department of Health (2014) The national cancer strategy: 4th annual report NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019)

Questions for consultation

Have all relevant comparators for gilteritinib been included in the scope?

Which treatments are considered to be established clinical practice in the NHS for treating relapsed or refractory FLT3-mutation positive acute myeloid leukaemia?

Is MEC (mitoxantrone, etoposide, cytarabine) a relevant comparator?

Would stem cell transplantation be a viable option at this point in the disease?

Are the outcomes listed appropriate?

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

Where do you consider gilteritinib will fit into the existing Blood and bone marrow cancers (2016) NICE pathway?

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 gilteritinib 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 gilteritinib 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 gilteritinib 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 December 2018.

