

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## GUIDANCE EXECUTIVE (GE)

### Review of TA218; Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia

This guidance was issued in March 2011.

The review date for this guidance is February 2014.

#### 1. Recommendation

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

#### 2. Original remit(s)

To appraise the clinical and cost effectiveness of azacitidine within its licensed indication for the treatment of patients with higher risk (IPSS intermediate-II risk and high-risk) myelodysplastic syndrome, chronic myelomonocytic leukaemia, and acute myeloid leukaemia (<30% blasts).

#### 3. Current guidance

1.1 Azacitidine is recommended as a treatment option for adults who are not eligible for haematopoietic stem cell transplantation and have:

- intermediate-2 and high-risk myelodysplastic syndromes according to the International Prognostic Scoring System (IPSS) **or**
- chronic myelomonocytic leukaemia with 10–29% marrow blasts without myeloproliferative disorder **or**
- acute myeloid leukaemia with 20–30% blasts and multilineage dysplasia, according to the World Health Organization classification **and**
- if the manufacturer provides azacitidine with the discount agreed as part of the patient access scheme.

#### **4. Rationale<sup>1</sup>**

No new evidence has been identified that is likely to lead to a change in the recommendations of the original guidance. We therefore propose that this guidance is placed on the 'static list'.

#### **5. Implications for other guidance producing programmes**

There is no proposed or ongoing guidance development that overlaps with this review proposal.

#### **6. New evidence**

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from March 2009 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

#### **7. Summary of evidence and implications for review**

Since the publication of TA218 in March 2011, no further NICE Technology Appraisals have been published in myelodysplastic syndrome. TA270 (Decitabine for the treatment of acute myeloid leukaemia) was terminated because the manufacturer did not provide an evidence submission. There is one related ongoing NICE Technology appraisal: 'Lenalidomide for the treatment of myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality in people with red blood cell transfusion dependence'. This appraisal is currently suspended because further cost-effectiveness analysis from the manufacturer is required. The scope for this appraisal has listed azacitidine and stem cell transplantation as comparators for people with intermediate-2 and high risk myelodysplastic syndrome.

#### **Clinical effectiveness evidence**

The manufacturer stated that it is not aware of any new evidence relevant to this appraisal at this point. The literature search for this review did not identify any new major trials or RCTs relevant to the recommendations made in TA218. Four ongoing/registered phase 3 trials were identified investigating azacitidine; however, the patient populations are not relevant to the recommendations made in TA218. The manufacturer has stated that there are no proposed licence extensions relevant to TA218.

No quality of life data were collected in the pivotal trial (AZA-001) underpinning TA218, and it was recommended in TA218 that further research was undertaken to estimate utility values using directly observed health-related quality of life values (such as EQ-5D scores). The literature search for this review did not identify any

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<sup>1</sup> A list of the options for consideration, and the consequences of each option is provided in Appendix 1 at the end of this paper

studies that would improve the uncertainty with regard to improvements in quality of life with azacitidine.

The literature search identified some sub-group analyses of the original trial considered in TA218 (AZA-001) plus observational and registry data on how it has been used in clinical practice. In addition, there are also some studies looking at the effect of changing the 7 day treatment schedule. Overall, there is no new clinical evidence identified that is likely to lead to a change in the recommendations of the original guidance.

### **Cost-effectiveness evidence**

The price of azacitidine has not changed since the publication of TA218 (that is, £321.00 per 100-mg vial). The Department of Health commented that the PAS is operating without any major problems, and the manufacturer confirmed that it is its intention to continue the existing PAS with TA218 without any changes.

When calculating the cost effectiveness of azacitidine, the Committee used a comparator consisting of the weighted average of conventional care (including best supportive care alone, low-dose chemotherapy plus best supportive care and standard-dose chemotherapy plus best supportive care). Best supportive care included blood transfusions, erythropoietin and granulocyte-colony stimulating factor, with infection prophylaxis and chemotherapy options included cytarabine and anthracyclines. It is unlikely that the cost of these treatments has changed to a degree that could lead to a change in the recommendations of the original guidance.

## **8. Implementation**

A submission from Implementation is included in Appendix 3.

## **9. Equality issues**

The Committee noted that azacitidine may be of specific benefit to those who, for clinical or religious reasons, are unable to receive blood transfusions, because patients treated with azacitidine require fewer blood transfusions than patients treated with best supportive care.

**GE paper sign off:** Elisabeth George, Associate Director, 30 01 14

### **Contributors to this paper:**

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## Appendix 1 – explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – ‘Yes/No’
A review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE’s work programme.	No
The decision to review the guidance should be deferred to [specify date or trial].	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal.	A review of the appraisal(s) will be planned into NICE’s work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE.	A review of the appraisal(s) will be planned into NICE’s work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	<p>The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review.</p> <p>This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.</p>	No
The guidance should be updated in an on-going clinical guideline.	<p>Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn.</p> <p>Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).</p>	No

Options	Consequence	Selected – ‘Yes/No’
The guidance should be transferred to the ‘static guidance list’.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes

NICE would typically consider updating a technology appraisal in an ongoing guideline if the following criteria were met:

- i. The technology falls within the scope of a clinical guideline (or public health guidance)
- ii. There is no proposed change to an existing Patient Access Scheme or Flexible Pricing arrangement for the technology, or no new proposal(s) for such a scheme or arrangement
- iii. There is no new evidence that is likely to lead to a significant change in the clinical and cost effectiveness of a treatment
- iv. The treatment is well established and embedded in the NHS. Evidence that a treatment is not well established or embedded may include;
  - Spending on a treatment for the indication which was the subject of the appraisal continues to rise
  - There is evidence of unjustified variation across the country in access to a treatment
  - There is plausible and verifiable information to suggest that the availability of the treatment is likely to suffer if the funding direction were removed
  - The treatment is excluded from the Payment by Results tariff
- v. Stakeholder opinion, expressed in response to review consultation, is broadly supportive of the proposal.

## Appendix 2 – supporting information

### Relevant Institute work

#### *Published*

Decitabine for the treatment of acute myeloid leukaemia (terminated appraisal). TA270. Published: December 2012.

Improving outcomes in haemato-oncology cancer. Cancer Service Guidance CSGHO. Published: October 2003.

#### *In progress*

Lenalidomide for the treatment of myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality in people with red blood cell transfusion dependence [ID480]. Referral: July 2011. Expected publication: TBC.

Suspended following the committee meeting 7 January 2014 because further cost-effectiveness analysis from the manufacturer is required and therefore NICE will not release an ACD on 27 January 2014.

#### *Referred - Qs and CGs*

Haematological malignancies. Quality standard referred to NICE.

### Details of changes to the indications of the technology

Indication considered in original appraisal	Proposed indication (for this appraisal)
<p>2.1 Azacitidine has a UK marketing authorisation for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation with:</p> <ul style="list-style-type: none"> <li>• intermediate-2 and high-risk myelodysplastic syndromes according to the International Prognostic Scoring System (IPSS)</li> <li>• chronic myelomonocytic leukaemia with 10–29% marrow blasts without myeloproliferative disorder <b>or</b></li> <li>• acute myeloid leukaemia with 20–30% blasts and multilineage dysplasia, according to World Health Organization classification.</li> </ul> <p>2.3 The list price of azacitidine is £321 for a 100-mg vial (excluding VAT; 'British national formulary' [BNF] edition 60). Based on a body surface area of 1.7 m<sup>2</sup> and a dose of 75 mg/m<sup>2</sup>, fourteen vials would be required for one cycle (two vials for each day of treatment). Costs may vary in different settings because of negotiated procurement discounts.</p> <p>2.4 The manufacturer had agreed a patient</p>	<p>No change to the indication.</p> <p>No change to the price. Source: BNF (December 2013)</p>

Indication considered in original appraisal	Proposed indication (for this appraisal)
<p>access scheme with the Department of Health in which azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia would be available with a discount applied to all invoices (referred to as the 'original' patient access scheme in this document). The manufacturer subsequently proposed a revised patient access scheme, in which the discount level is revised and is commercial-in-confidence (see section 5.3). The Department of Health has agreed that the revised patient access scheme can be included in this appraisal in January 2011. The manufacturer has agreed that the revised patient access scheme will remain in place until the publication of reviewed NICE guidance.</p>	

### Details of new products

Drug (manufacturer)	Details (phase of development, expected launch date, )
ACE-536 (Acceleron)	<p>Myelodysplastic syndromes Phase II clinical trials</p>
Ceplene (Meda Pharmaceuticals)	<p>Ceplene maintenance therapy is indicated for adult patients with acute myeloid leukaemia in first remission concomitantly treated with interleukin-2 (IL-2). Marketing authorisation: October 2008</p>
Cytarabine + daunorubicin liposomal (Celator)	<p>Acute myeloid leukaemia Phase III clinical trials ██████████</p>
Darbepoetin alfa (Amgen)	<p>Myelodysplastic syndromes Phase III clinical trials ██████████</p>
Midostaurin (Novartis)	<p>Acute myeloid leukaemia - newly diagnosed patients, &lt;60 years, FLT3 mutation Phase III clinical trials ██████████</p>
Quizartinib (Ambit BioSciences)	<p>Acute myeloid leukaemia Phase II clinical trials</p>
Rigosertib (Baxter)	<p>Myelodysplastic syndromes</p>

<b>Drug (manufacturer)</b>	<b>Details (phase of development, expected launch date, )</b>
	Phase III clinical trials ██████████
Sapacitabine (Cyclacel Pharmaceuticals)	Acute myeloid leukaemia Phase II clinical trials
Tosedostat (Cell Pathways)	Acute myeloid leukaemia - relapsed or refractory Phase II clinical trials
Volasertib (Boehringer Ingelheim)	Acute myeloid leukaemia - 1st-line, aged >64 Phase III clinical trials ██████████
Vosaroxin (Sunesis)	Acute myeloid leukaemia Phase III clinical trials ██████████

### Registered and unpublished trials

<b>Trial name and registration number</b>	<b>Details</b>
A Phase 3, Multicenter, Randomized, Open-Label, Study of Azacitidine (Vidaza) Versus Conventional Care Regimens for the Treatment of Older Subjects With Newly Diagnosed Acute Myeloid Leukemia NCT01074047 Phase 3	Status: ongoing, not recruiting Eligibility: bone marrow blasts >30% Expected enrolment: 480 Expected completion: February 2015
Randomized Controlled Study of Post-transplant Azacitidine for Prevention of Acute Myelogenous Leukemia and Myelodysplastic Syndrome Relapse NCT00887068 Phase 3	Status: recruiting Method: open label, single group Expected enrolment: 277 Expected completion: April 2015

Trial name and registration number	Details
<p>A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Compare Efficacy and Safety of Oral Azacitidine Plus Best-supportive Care Versus Best Supportive Care as Maintenance Therapy in Subjects With Acute Myeloid Leukemia in Complete Remission</p> <p>NCT01757535</p> <p>Phase 3</p>	<p>Status: recruiting</p> <p>Expected enrolment: 460</p> <p>Expected completion: February 2018</p>
<p>A Phase 3, Multicenter, Randomized, Double-blind Study to Compare the Efficacy and Safety of Oral Azacitidine Plus Best Supportive Care Versus Placebo Plus Best Supportive Care in Subjects With Red Blood Cell Transfusion-dependent Anemia and Thrombocytopenia Due to IPSS Lower-risk Myelodysplastic Syndromes</p> <p>NCT01566695</p> <p>Phase 3</p>	<p>Status: recruiting</p> <p>Expected enrolment: 386</p> <p>Expected completion: December 2016</p>

## Appendix 3 – Implementation submission

### 1. Routine healthcare activity data

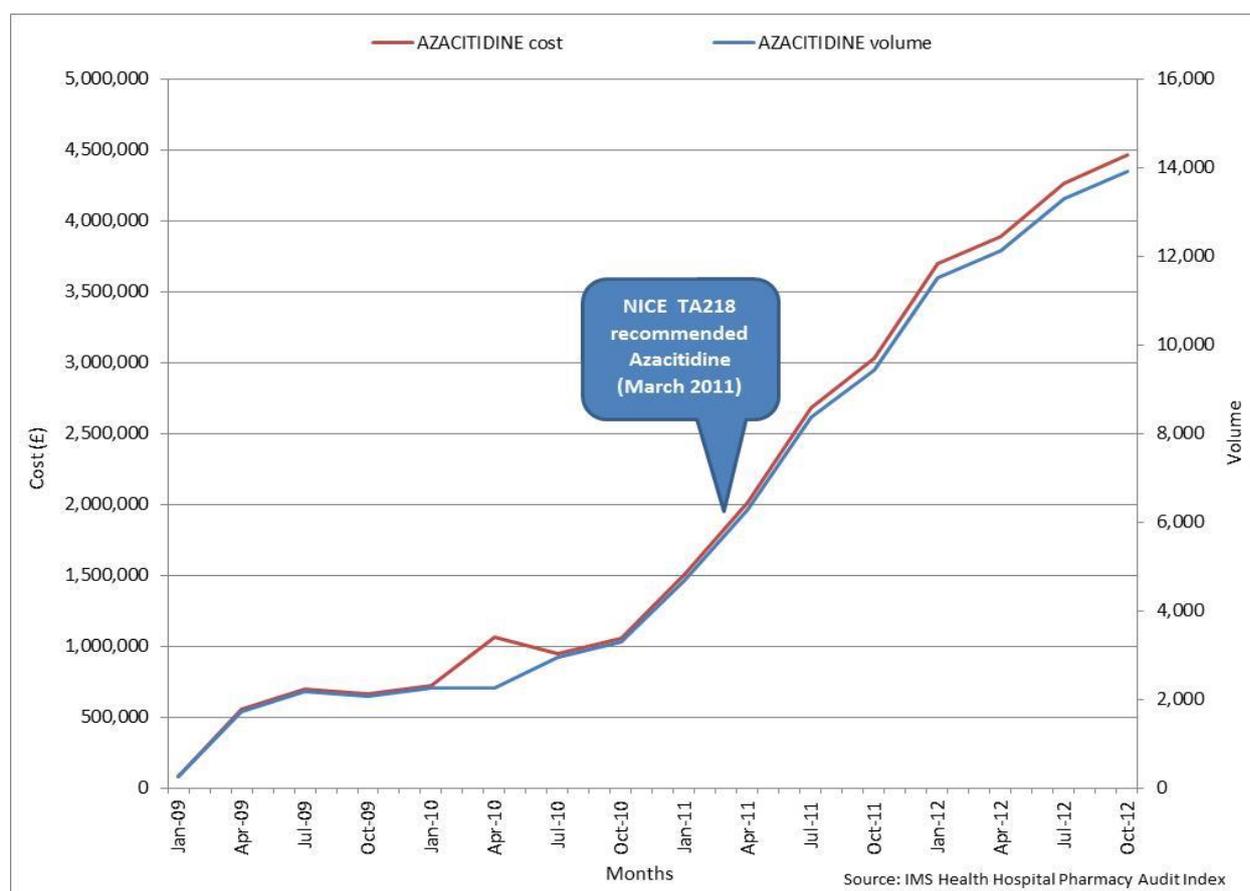
#### 1.1. ePACT data

The electronic prescribing analysis and cost tool (ePACT) system produced zero data on the net ingredient cost and volume of Azacitidine, suggesting that this drug is not prescribed and dispensed in primary care or the community.

#### 1.2. Hospital Pharmacy Audit Index data

This section presents hospital pharmacy audit index data on the net ingredient cost and volume of Azacitidine prescribed and dispensed by hospital pharmacies in England between January 2009 and December 2012.

**Figure 1 Cost and volume of Azacitidine prescribed and dispensed in hospitals in England**



### 2. Implementation studies from published literature

Information is taken from the [uptake database](#) website.

Nothing specific to add.

### **3. Qualitative input from the field team**

***The implementation field team have recorded the following feedback in relation to this guidance:***

Nothing specific to add.