National Institute for Health and Clinical Excellence

Azacitidine for the treatment of myelodysplastic syndrome, chronic myelomonocytic leukaemia, and acute myeloid leukaemia

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	CLIC Sargent	Appropriate	Comment noted
	Royal College of Physicians	Appropriate	Comment noted
	Cardiff and Vale NHS Trust	This is an important new treatment modality for MDS. It is imperative that NICE reviews this with some urgency.	Comment noted
	Rarer Cancers Forum	It is appropriate for NICE to consider this drug. It is a small population that will ever require the treatment and it comes under the umbrella of an orphan drug. In this case we wonder why NICE spends funds assessing this drug it should be given its orphan status.	Comment noted
	Celgene Ltd	The topic is appropriate. There are no licensed products for the treatment of MDS in the UK and the current treatment for MDS is best supportive care. Azacitidine is likely to be the first licensed treatment for MDS and is the only therapy to have demonstrated a significant survival advantage and a significant improvement in quality of life compared to conventional care. Azacitidine is the first of a new class of anti-cancer compounds known as epigenetic therapies. Azacitidine represents a new approach to treating cancer, rather than using molecules that kill both normal, and tumour cells, silenced genes are reactivated through targeted therapy, re-establishing the cancer cell's natural mechanisms to control abnormal growth. Epigenetic therapy is less toxic than many forms of chemotherapy and is generally more convenient to administer. The draft remit/appraisal objective described in this scope needs to be specific to the licensed indication for azacitidine which is as described in the "Wording" section below.	Scope amended to ensure the remit reflects the anticipated licensed indication
Wording	CLIC Sargent	Agree	Comment noted
	Royal College of Physicians	To appraise the clinical and cost effectiveness of azacitidine within its licensed indication for the treatment of patients with high-risk myelodysplastic syndrome and acute myeloid leukaemia (<30% blasts).	Comment noted

Section	Consultees	Comments	Action
	Cardiff and Vale NHS Trust	No comments	Comment noted
	Rarer Cancers Forum	Agree	Comment noted
	Celegene Ltd	The wording of the draft remit deserves some clarifications to reflect the licensed indication accuratedly To appraise the clinical and cost effectiveness of azacitidine within its licensed indication for the treatment of patients with: • Intermediate-2 and High-risk Myelodysplastic Syndromes (MDS) according to the International Prognostic Scoring System (IPSS), • Chronic Myelomonocytic Leukemia (CMMoL (10%-29% marrow blasts without Myeloproliferative Disorder)), • Acute Myeloid Leukemia (AML) with 20-30% blasts and multi-lineage dysplasia, according to World Health Organisation Classification (WHO).	Scope amended to ensure the remit reflects the anticipated licensed indication
Timing Issues	CLIC Sargent	CLIC Sargent believes that in light of ongoing plans to study for azacitidine in a paediatric population NICE should consider any future evidence supporting the use of this technology for the treatment of MDS and AML in children. Although data on paediatrics will come later than the evidence for the use of azacitidine in adults, NICE should not delay the evaluation in adults, just not preclude examining subsequent use in children.	Comment noted
	Royal College of Physicians	Relatively urgent given the poor prognosis of these disorders and the orphan disease status. This is an unmet clinical need.	Comment noted
	Cardiff and Vale NHS Trust	Urgent	Comment noted
	Rarer Cancers Forum	There are patients who experience a poorer quality of life without this treatment and it is needed	Comment noted
	Celgene Ltd	Timing of the scoping process is appropriate	Comment noted
Additional comments on the draft remit	CLIC Sargent	No comments	Comment noted
	Royal College of Physicians	No comments	Comment noted

Section	Consultees	Comments	Action
	Cardiff and Vale NHS Trust	No comments	Comment noted
	Rarer Cancers Forum	No comments	Comment noted
	Celgene Ltd	No comments	Comment noted

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	CLIC Sargent	The draft scope does not include a reference to the incidence of MDS and AML in children and young people. There are approximately 100 new cases of AML in children each year in the UK. AML can affect children of any age, and girls and boys are affected equally.	The use of azacitidine in children is not covered by this appraisal as it is not anticipated that azacitidine will be licensed for use in children in the UK
	Royal College of Physicians	Para 3: suggest "Such high risk MDS or AML subgroups with <30% blasts corresponds to refractory anaemia with excess blasts (5-20% blasts) or refractory anaemia with excess blasts in transformation (RAEB-T), as defined under the French-American-Britain (FAB) classification system." Useful to state approximate patient numbers in this subgroup, namely 30% of MDS patients defined by FAB subgroups (RAEB plus RAEB-t); data from Dusseldorf MDS registry. Therefore approximately 660 new diagnoses per annum and a prevalence of < 660 given the median survival for IPSS INT-2/High combined of < 1year.	Amendments have been made to the background section following consultation on the scope
	Cardiff and Vale NHS Trust	Basic but generally accurate. Good be substantially increased to give a full picture. No explicit reference is made to monosomy 7 patients.	The background section has been amended following consultation on the scope. The scope also now states that, if the evidence allows, consideration will be given to the subgroup of patients with chromosome 7 abnormalities
	Rarer Cancers Forum	There seems little about the side effects of the current treatment options The prognosis of MDs patients is poor with 30% progressing to AML but 40% of patients die of other disease complications such as infection or haemorrhage hence the need for alternative therapy.	Complications such as severe infections are now referred to in the background section.

Section	Consultees	Comments	Action
	Celgene Ltd	The background information requires additional information to convey the severity of the disease and in particular the severity in those in the higher risk subgroups. A proposed wording based on the draft background and with some additional information is included below. This description also includes the proportions of patients affected by higher risk disease where the licensed indication and proposed utility of azacitidine is most relevant: The Myelodysplastic syndromes (MDS) are a diverse group of haematological disorders in which the bone marrow functions abnormally and insufficient numbers of mature blood cells are produced. Red blood cells, white blood cells platelets may all be affected by MDS, resulting in life threatening disease, with anaemia and increased risk of bleeding and infections. MDS takes a heavy toll on patients' quality of life due to debilitating symptoms such as fatigue and dyspnoea, onerous treatment regimens involving hospitalisation with intravenous drug infusions and blood transfusions; and complications such as severe infections. MDS are associated with an increased risk of transformation to acute myeloid leukaemia (AML), which is a progressive form characterised by rapidly growing cancer of the blood and bone marrow. 30% of patients with MDS will progress to AML, which is the commonest type of acute leukaemia in adults. MDS is predominantly a condition of the elderly. There were 1,993 people newly diagnosed with MDS in England in 2004, with over 90% of patients aged over 60 at the time of diagnosis. Men are more likely than women to have MDS. Median survival of all MDS subtypes is around 20 months, however median survival in high risk subgroups can be less than six months. High risk subgroups of MDS patients are defined on the basis of the proportion of blasts, cytogenetics and blood cytopenia under the International Prognostic Scoring System (IPSS) to predict disease progression. The mainstay of treatment for MDS is best supportive care (transfusions, growth factors, antibiotics) to control the symptoms of bone marrow failure, and low dose or standard chemotherapy for some patients. Stem Cell Transplant is not an option for the majority of patients since in most cases the patients' age and/or co-morbidities preclude this treatment option.	The background section has been updated following consultation on the scope
The	CLIC Sargent	Yes	Comment noted

Section	Consultees	Comments	Action
technology/ intervention	Royal College of Physicians	Azacitidine is administered subcutaneously or intravenously.	Technologies are appraised within their licensed indications, and it is not anticipated that azacitidine will be licensed for intravenous use in the UK.
	Cardiff and Vale NHS Trust	Agree	Comment noted
	Rarer Cancers Forum	Agree	Comment noted
	Celgene Ltd	Yes, although the licensed indications needs to be defined as for treatment of patients with: • Intermediate-2 and High-risk Myelodysplastic Syndromes (MDS) according to the International Prognostic Scoring System (IPSS), • Chronic Myelomonocytic Leukemia (CMMoL (10%-29% marrow blasts without Myeloproliferative Disorder)), • Acute Myeloid Leukemia (AML) with 20-30% blasts and multi-lineage dysplasia, according to World Health Organisation Classification (WHO).	Scope amended to ensure the remit reflects the anticipated licensed indication
Population	CLIC Sargent	Children and young people should be included in the scope of this assessment and NICE may wish to consider them as a sub-group for this appraisal.	Technologies are appraised within their current licensed indications, and it is not anticipated that azacitidine will be licensed for use in children in the UK
	Royal College of Physicians	Yes, but should include all IPSS INT-2/High patients, some of whom may have <5 blasts; see answers to specific questions below.	The scope has been amended to include IPSS INT-2/High patients
	Cardiff and Vale NHS Trust	Consider patients with monosomy 7 as a separate group.	The scope now states that, if the evidence allows, consideration will be given to the subgroup of patients with chromosome 7 abnormalities

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	Rarer Cancers Forum	This is small group of patients with an orphan cancer.	Comment noted
	Celgene Ltd	Described below are the proportions of patients affected by higher risk disease (Int-2 and High risk based on IPSS score) where the licensed indication and proposed utility of azacitidine is most relevant The higher risk MDS subgroups with IPPS score Intermediate-2 or High risk form 22% and 7% of the MDS population respectively. In this group of patients and those with CMMoL (10%-29% marrow blasts without Myeloproliferative Disorder) and AML (with 20-30% blasts and multi-lineage dysplasia, bone marrow failure is much more rapid and cytopenias more frequent, leading to rapid deterioration and risk of infection, bleeding and death. The aim of treatment in this group is to alter the natural history of the disease and prolong survival and improve the quality of survival rather than only providing supportive care and managing symptoms.	Amendments have been made to the background section following consultation on the scope
Comparators	CLIC Sargent	In terms of comparators, it is important to bear in mind that the comparator studies in adults may not be feasible or ethical in children and there is a greater use of historical controls. The definitions of the appropriate target group in paediatric AML and MDS are likely to differ from those used in adults and are still being defined.	The use of azacitidine in children is not covered by this appraisal as it is not anticipated that azacitidine will be licensed for use in children in the UK
	Royal College of Physicians	Stem cell transplantation is not strictly a valid comparator as a) none of the trials have made a comparison with SCT and b) SCT is curative therapy and Azacitidine is not. However SCT is considered increasingly in older patients with reduced intensity conditioning, and is currently being explored following Azacitidine therapy.	The scope has been amended to remove stem cell transplant from the list of comparators
	Cardiff and Vale NHS Trust	Best supportive care is blood/platelet transfusion as required with infection propylaxis. Few patients are suitable for chemotherapy or bone marrow transplantation.	The scope states that the mainstay of treatment for MDS is best supportive care and low dose or standard chemotherapy for some patients. Stem cell transplant has been removed from the list of comparators

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	Rarer Cancers Forum	At present there is no single agent or combination therapy that is seen as standard for MDS in the UK or the EU. There is obviously an unmet need. This therapy improves overall survival but it also offers better quality of life with patients needing fewer transfusions getting fewer infections and fewer bleeding episodes. Bone marrow failure is reduced. The impact of these complications is overwhelming for patients and the therapy offers better quality of life than best supportive care.	Comment noted

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	Celgene Ltd	Best supportive care (BSC) The mainstay of treatment for MDS is BSC. In the majority of patients with MDS, BSC aims to control the symptoms of BM failure and improve the QoL of the patient, primarily through red blood cells (RBCs) and/or transfusions, antibiotics and, to a limited extent, cytokines, erythropoietin (EPO) or granulocytic growth factors. All patients, in the registration study received BSC. Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor were permitted based on criteria described in the protocol, but EPO was not allowed during the course of the study. Stem Cell Transplantation Stem cell transplantation (SCT) is not an appropriate comparator for Vidaza. SCTs are only an option for a relatively small proprotion of MDS patients. An inclusion criteria in the pivotal phase III trial (AZA-001) on which we have made our marketing authorisation (license) application to European Medicines Agency (EMEA) was that patients should "Be unlikely to proceed to bone marrow or stem cell transplantation therapy following remission". [redacted] In the pivotal phase III trial (AZA-001) patients were randomized to either receive azacitidine or a conventional care regimen, assigned at the discretion of their individual study investigator prior to randomisation. The conventional care regimin consisted of 3 options: • Best Supportive Care (BSC) only; • Low-Dose cytarabine plus BSC; or • Standard chemotherapy plus BSC. This approach was taken because not all patients are suitable for either Low-Dose cytarabine or standard chemotherapy. We agree that BSC is the most appropriate standard comparator for the licensed indication. Further low-dose cytarabine plus BSC is an appropriate compatator for a sub-group of patients in the licensed indication, but is not a standard comparator for all patients.	Following the workshop it was agreed that EPO should remain in the scope as a component of best supportive care. The scope has been amended to exclude stem cell transplant from the list of comparators. The scope has been amended to distinguish between low and high dose chemotherapy.

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	Celgene continued	Equally, standard chemotherapy consisting of cytarabine and an anthracycline plus BSC is also an appropriate comparator for a sub-group of patients, but is not a standard comparator for all patients.	
Outcomes	CLIC Sargent	Agree	Comment noted
	Royal College of Physicians	Agree	Comment noted
	Cardiff and Vale NHS Trust	Agree	Comment noted
	Rarer Cancers Forum	We are very keen that the outcomes consider the impact on quality of life for at present the current therapies including best supportive care.	Health-related quality of life is included as an outcome
	Celgene Ltd	The outcome measures to be considered should include: • overall survival • Time to AML or Death • Time to AML • Haematologic response and improvement • Transfusion independence • Infections requiring IV therapy • Safety • adverse effects of treatment • health-related quality of life.	The scope has been amended to include time to AML or death; haematologic response and improvement; transfusion independence; and infections requiring IV therapy.
Economic analysis	CLIC Sargent	No comments	Comment noted
	Royal College of Physicians	Acceptable	Comment noted
	Cardiff and Vale NHS Trust	2 years	Comment noted
	Rarer Cancers Forum	These patients without this therapy require repeated blood transfusions at a time when there is limited availability to blood and rising costs of these procedures to healthcare providers and this therapy reduces the dependence and the cost of repeated transfusions.	The scope has been amended to include transfusion independence as an outcome.

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	Celgene Ltd	No comments.	Comment noted
Equality	CLIC Sargent	The assessment of azacitidine should take full account of children and young people with AML as a group with distinct needs from those of adult patients.	Technologies are appraised within their current licensed indications, and it is not anticipated that azacitidine will be licensed for use in children in the UK.
	Royal College of Physicians	None anticipated	Comment noted
	Cardiff and Vale NHS Trust	Adequate funding. This will be expensive treatment.	Comment noted
	Rarer Cancers Forum	As the NHS we need to offer patients the best treatment possible at the time of need These patients are certainly in a time of need.	Comment noted
	Celgene Ltd	No comments	Comment noted
Other considerations	CLIC Sargent	No comments	Comment noted
	Royal College of Physicians	None	Comment noted
	Cardiff and Vale NHS Trust	Benefit of the drug in offsetting blood transfusion, and the complications or transfusion including iron loading (and its treatment) and immunosuppression.	The scope has been amended to include transfusion independence as an outcome
	Rarer Cancers Forum	No comments	Comment noted
	Celgene Ltd	No comments	Comment noted

Section	Consultees	Comments	Action
Questions for consultation	CLIC Sargent	CLIC Sargent believes that: 1. A single technology appraisal is appropriate for this assessment 2. Children and young people are an important group, which ought to be included in the scope of this assessment, potentially as a sub-group.	Comment noted Technologies are appraised within their current licensed indications, and it is not anticipated that azacitidine will be licensed for use in children in the UK
	Royal College of Physicians	What are the implications of different classification systems of myelodysplastic syndromes for defining the population to be included? Is the population correctly defined in the draft scope? --the definition of high-risk MDS should include all patients with IPSS INT-2/High. Some patients will have <5% blasts and will be RA (RS) or RCMD (RS). Such patients will have an adverse karyotype and will include those with chromosome 7 abnormalities. Several studies indicate a superior response rate in patients with chromosome 7 disorders. Despite the reclassification of RAEB-t to AML in the WHO classification, it remains appropriate to include such patients as they were treated in the 001 survival study. Have the most appropriate comparators for the treatment of MDS and AMD (<30% blasts) been included in the scope?--Yes Which chemotherapy regimens are routinely used in clinical practice?--Intensive chemotherapy comprises combinations of an anthracycline and Cytosine arabinoside ("DA") sometimes with Etoposide ("ADE"). Low intensity regimens are low dose cytosine arabinoside per 001 study. Is stem cell transplantation an appropriate comparator? --probably not; see comments above How should best supportive care be defined? --red cell and platelet transfusion, days in hospital and antibiotic use. Some patients will receive G-CSF and rarely Erythropoietic stimulating agents. Are there any subgroups of patients in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately?--chromosome 7 abnormal.	The scope has been amended to include IPSS INT-2/High patients. The scope also now states that, if the evidence allows, consideration will be given to the subgroup of patients with chromosome 7 abnormalities The comparators have been revised
	Cardiff and Vale NHS Trust	No comments	Comment noted

Section	Consultees	Comments	Action
	Rarer Cancers Forum	No comments	Comment noted
	Celgene Ltd	Classification systems in draft scope: The proposed amendments described in other sections ensure correct definition of the population, the classification systems are described below: The FAB classification classifies MDS into five subtypes: Refractory anaemia (RA): <5% blasts in BM and <1% blasts in peripheral blood. RA with ringed sideroblasts (RARS): defined as RA as above, but also including the presence of ≥15% ringed sideroblasts in BM. RA with excess blasts (RAEB): 5-20% blasts in BM and <5% blasts in peripheral blood. RAEB in transformation (RAEB-T): 21-30% blasts in BM and ≥5% blasts in peripheral blood, or presence of Auer rods in the blasts. Chronic myelomonocytic leukaemia (CMML): ≤20% blasts in BM, <5% blasts in peripheral blood and absolute monocytosis (>1 x 10^9/l). The WHO classification for MDS was published in 2001 with the aim of further improving the prognostic value of MDS classification. Using the FAB classification as its backbone, the WHO classifies MDS into eight subtypes: RA. RARS. Refractory cytopenia with multi-lineage dysplasia (RCMD). RCMD and ringed sideroblasts (RCMD-RS). RAEB-1. RAEB-2. MDS unclassified (MDS-U). MDS associated with isolated del(5q) In terms of differences between the two, in the WHO system RAEB-T (from FAB) are now classified as AML and CMMoL have been excluded from WHO classification of MDS and form a separate WHO group but both of these conditions with blast counts of <30% behave similarly to MDS, patients with these conditions were included in our pivotal phase III study (AZA-001) and	Comments noted

Section	Consultees	Comments	Action
		thus are included in the proposed licensed indication for azacitidine. The IPSS groups included in the proposed licensed indication are Intermediate-2 and High-risk Myelodysplastic Syndromes (MDS) according to the International Prognostic Scoring System (IPSS).	
	Celgene continued	The IPSS provides a tool for physicians to evaluate and treat patients according to the actual prognosis of their disease, it also provides a survival prognosis MDS patients based on their score, which is either low, intermediate-1, intermediate-2 and high risk.	Comment noted
Additional comments on the draft scope.	CLIC Sargent	No comments	Comment noted
	Royal College of Physicians	No comments	Comment noted
	Cardiff and Vale NHS Trust	No comments	Comment noted
	Rarer Cancers Forum	No comments	Comment noted
	Celgene Ltd	Azacitidine was designated as an orphan medicinal product by the EMEA for the treatment of MDS on 14th January 2003 Azacitidine was additionally designated as an orphan medicinal product by the EMEA for the treatment of AML on 13th December 2007.	Comments noted

Comment 4: Regulatory issues

Section	Consultees	Comments	Action
Draft remit	Celgene Ltd	[redacted]	Scope amended to ensure the remit reflects the anticipated licensed indication

Section	Consultees	Comments	Action
Current or proposed marketing authorisation	Celgene Ltd	*What are the current indications for the technology?* [redacted] *What are the planned indications for the technology?* [redacted] *What is the target date for regulatory submission?* [redacted] *Which regulatory process are you following?* [redacted] *Please indicate whether information provided is CIC?* [redacted]	Scope amended to ensure the remit reflects the anticipated licensed indication

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

Royal College of Nursing
Welsh Assembly Government
Macmillan Cancer Support
Royal Pharmaceutical Society
Sanofi-Aventis
NHS Quality Improvement Scotland