Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

Azacitidine 100mg powder for suspension for injection (Vidaza®)

SMC No. (589/09)

Celgene Ltd

05 August 2011

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

azacitidine (Vidaza®) is accepted for use within NHS Scotland.

Indication under review: for treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (SCT) with intermediate-2 and high-risk myelodysplastic syndrome (MDS), chronic myelomonocytic leukaemia (CMML) or acute myeloid leukaemia (AML).

Azacitidine therapy produced a significant increase in overall survival compared with conventional care regimens in previously untreated higher-risk MDS patients.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of azacitidine. This SMC advice is contingent upon the continuing availability of the PAS in NHS Scotland.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 12 September 2011

Indication

Treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (SCT) with:

- intermediate-2 and high-risk myelodysplastic syndrome (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 multilineage dysplasia, according to the World Health Organisation classification

Dosing Information

Azacitidine 75mg/m^2 subcutaneously daily for seven days followed by a rest period of 21 days (28 day treatment cycle). It is recommended that patients are treated for a minimum of six cycles. Treatment should be continued as long as the patient continues to benefit or until disease progression.

Azacitidine treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic agents. Patients should be pre-medicated with anti-emetics for nausea and vomiting.

Product availability date

2 March 2009

Designated Orphan Medicine in European Union for the treatment of MDS and AML.

Summary of evidence on comparative efficacy

Myelodysplastic syndrome (MDS) is a rare and life-threatening disease affecting 4 per 100,000 of the general population with the incidence increasing with age. MDS comprises a heterogeneous group of haematological disorders characterised by progressive cytopenias, complications of infection and bleeding and a risk of progression to AML.

Azacitidine is a pyrimidine analogue which blocks the synthesis of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) and therefore inhibits the growth of tumour cells. Azacitidine is also thought to inhibit tumour growth through inhibition of DNA-methylation (hypomethylation). Azacitidine has been designated an orphan medicine for the treatment of MDS and AML in the European Union.

One pivotal open-label study has compared the efficacy of azacitidine and conventional care regimens (CCR) in previously untreated adult patients with high-risk MDS who were considered unlikely to proceed to bone marrow or stem cell transplantation following remission. Eligible patients had a life expectancy of at least 3 months and an Eastern Co-operative Oncology Group (ECOG) performance status of 0 to 2. They had higher risk MDS (IPSS rating of intermediate-2 or high risk) and French-American-British (FAB) defined refractory anaemia with excess blasts, refractory anaemia with excess blasts in transformation or CMML. Before

randomisation, treating physicians selected which of three CCRs was most appropriate for the individual patient based on age, ECOG performance status and co-morbidities. Patients (n=358) were then randomised, with stratification for FAB and IPSS classifications, to receive azacitidine (75mg/m^2 subcutaneously daily for 7 days every 28 days for at least six cycles) or CCR. The three CCR options were best supportive care (BSC) alone (including blood product transfusions and antibiotics with growth factors for neutropenic infections); low-dose cytarabine (20mg/m^2 subcutaneously daily for 14 days every 28 days for at least four cycles) or intensive chemotherapy (induction with cytarabine 100 to 200mg/m^2 by continuous intravenous infusion daily for 7 days plus 3 days of either intravenous daunorubicin [45 to 60mg/m^2 daily], idarubicin [9 to 12mg/m^2 daily] or mitoxantrone [8 to 12mg/m^2 daily]). Patients in the latter group achieving a complete or partial remission after induction received one or two consolidation courses followed by BSC. All patients could receive BSC as needed. Numbers of patients randomised to investigator preselected subgroups were as follows: BSC alone (n=222; 117 patients randomised to azacitidine and 105 to BSC); low-dose cytarabine (n=94; 45 patients randomised to azacitidine and 49 to low-dose cytarabine) and intensive chemotherapy (n=42; 17 patients randomised to azacitidine and 25 to intensive chemotherapy).

The primary endpoint was overall survival between the azacitidine and combined CCR groups in the intention to treat (ITT) population. After a median follow-up of 21.1months, and a median of nine cycles of azacitidine, four and a half cycles of low dose cytarabine and one cycle of intensive chemotherapy, the median Kaplan-Meier overall survival was 24.5 months in the azacitidine group and 15.0 months in the CCR group corresponding to an absolute difference of 9.4 months and a hazard ratio of 0.58 (95% confidence intervals (CI): 0.43 to 0.77). There was a consistent survival benefit with azacitidine in all predefined subgroups of patients. Kaplan-Meier estimates of survival at two years were significantly higher in the azacitidine compared with the CCR group (51% versus 26% respectively). Survival benefits with azacitidine were found with each of the three CCR options (BSC alone [n=222]: 21.1 months versus 11.5 months respectively; low-dose cytarabine [n=94]: 24.5 months versus 15.3 months, respectively; and intensive chemotherapy [n=42]: 25.1 months versus 15.7 months, respectively). However in the intensive chemotherapy subgroup, the difference between treatments did not reach statistical significance.

The secondary endpoint of time to transformation to AML was 17.8 months in the azacitidine group and 11.5 months in the CCR group corresponding to a hazard ratio of 0.50 (95% CI: 0.35 to 0.70). The treatment difference was only significant for azacitidine in the subgroup of patients receiving BSC alone.

Overall remission (complete and partial) as reported by the investigator was significantly higher in azacitidine than in CCR patients (29% versus 12% respectively). However when assessed by the independent review committee (IRC) was 7% versus 1% respectively. This difference was due to the use of different criteria: the IRC using the International Working Group criteria which required improvement and maintenance of peripheral blood counts for at least 56 days. The investigator-assessed overall remission rate was higher with azacitidine than each of the preselected CCR subgroups except the intensive chemotherapy subgroup (29% versus 40% respectively).

Summary of evidence on comparative safety

In the pivotal study, the most common treatment-emergent adverse events were haematological toxicities including thrombocytopenia (70% azacitidine and 34% BSC patients), neutropenia (66% and 28% respectively), anaemia (51% and 44% respectively), leucopenia (18% and 2.0% respectively) and febrile neutropenia (14% and 9.8% respectively). In the azacitidine group these events were mainly grade 3 or 4 severity and were most frequent during the first two cycles of treatment. The most common non-haematological treatment-related adverse events were injection site reactions with azacitidine and nausea, vomiting, fatigue and diarrhoea with azacitidine, low dose cytarabine and intensive chemotherapy. The risk of infection requiring intravenous antimicrobials was lower in the azacitidine group than in patients treated with CCR (0.60 versus 0.92 per patient years respectively).

Summary of clinical effectiveness issues

Azacitidine is the first medicine to be licensed specifically for the treatment of primary MDS and is the first to demonstrate survival benefit in this disease. The Kaplan-Meier survival curves for azacitidine and CCR indicate that the survival benefit is seen after about three months. However, prior to three months, it would appear that survival was slightly higher in the CCR group. The survival benefit was seen in each of the investigator pre-selected subgroups of CCR. However, although the overall survival was longer in the azacitidine treated patients compared with the intensive chemotherapy treated patients, the difference did not reach statistical significance, possibly due to the small patient numbers.

The pivotal study was open-label and may have introduced the potential to bias the results. In addition, the study design, which allowed investigators to pre-select the most appropriate CCR for the individual patient, resulted in small patient numbers in the intensive chemotherapy group and some expected imbalances in the baseline characteristics between subgroups e.g. patients selected to receive intensive chemotherapy were younger and had better ECOG performance status and higher risk disease.

The pivotal study only assessed efficacy in patients with primary MDS and it is not known whether there would be any difference in patients with secondary disease.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing azacitidine plus BSC with three CCR regimens (BSC alone, low-dose cytarabine plus BSC and intensive chemotherapy plus BSC) in patients with MDS as per the licensed indication. A lifetime Markov model was used which consisted of three health states covering MDS, AML and death. Overall survival data were taken from the pivotal study and extrapolated over the lifetime of the model using the Weibull approach.

Utility values for the azacitidine and BSC arms of the model were obtained from mapping cancer-specific quality of life values from another MDS study to EQ-5D. Utility values for the low-dose cytarabine and intensive chemotherapy arms of the model were derived from a

separate study of chemotherapy patients which collected SF-12 data and these scores were then mapped to EQ-5D. Resource use was estimated using information obtained from a survey of Scottish clinicians or in some cases from information from the key clinical study.

A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered on the list price of azacitidine. When the PAS was incorporated into the analysis, the incremental cost per QALY was £51,275 based on an incremental cost of £55,787 and a QALY gain of 1.09.

Sensitivity analysis indicated that the results were sensitive to alternative methods of extrapolating benefits in the model and also to the utility values employed. If an exponential curve was used to extrapolate long-term survival the incremental cost effectiveness ratio (ICERs) rose to £55,654. Using a range of 0.6 to 0.8 for the mapped utility values, the ICERs ranged from £49,921 to £66,561 per QALY.

In addition to the comparatively high ICER, there were a number of limitations with the analysis:

- While the survival benefit over the CCR arm of the trial was statistically significant, in the comparison with intensive chemotherapy the difference in overall survival was numerically, but not statistically, significant. This numerical difference was applied in the economic model, which could be seen as a weakness It should however be noted that patient numbers were small in this analysis and the study not powered to detect a difference in this group of patients.
- No quality of life data were collected in the trial and there were some weaknesses with both the method used to derive the utility values and the generalisability of the azacitidine utility values to azacitidine-treated patients in all pre-selected subgroups. Given patients were assigned to the pre-selected subgroups on the basis of age, performance status and co-morbidities, it is possible that quality of life may differ between the azacitidine-treated groups. The sensitivity analysis indicated that there was some sensitivity to the assumptions regarding quality of life scores.

SMC considered the likely range of cost-effectiveness ratios and the uncertainties above. Although there were some limitations in the economic analysis, the economic case was considered demonstrated when the orphan status of the medicine was considered and SMC modifiers, in particular those relating to the improvement in life expectancy were applied.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

A Patient Interest Group Submission was received from MDS UK Patient Support Group: Leukaemia Care: (Joint Submission).

Additional information: guidelines and protocols

The British Committee for Standards in Haematology published a consensus guideline "Guidelines for the diagnosis and therapy of adult myelodysplastic syndromes" in 2003. This guideline predates the licensing of azacitidine and makes no specific recommendations on its use. Patients with IPSS intermediate-2 or high-risk MDS who are either >65 years or < 65 years but not eligible for stem cell transplantation should be considered for intensive chemotherapy alone.

The American National Comprehensive Cancer Network (NCCN) published "Myelodysplastic syndromes" in 2011. This guideline recommends azacitidine as an option for IPSS intermediate-2 and high-risk MDS patients not undergoing transplant and may also be used as a bridge to transplant while awaiting donor availability.

European Society of Medical Oncology (ESMO) published "Acute myeloblastic leukaemias and myelodysplastic syndromes in adult patients: ESMO clinical practice guidelines for diagnosis, treatment and follow-up" in 2010. This guideline recommends azacitidine as a possible treatment option for MDS patients and notes that azacitidine has demonstrated survival benefit over low-dose cytarabine or BSC, particularly in patients with chromosome 7 alterations.

Additional information: comparators

In patients with higher risk MDS who are ineligible for stem cell transplantation, the main comparator is intensive chemotherapy using agents not specifically licensed for MDS. Many patients will not be eligible for intensive chemotherapy but be managed by BSC or within a clinical trial.

Cost of relevant comparators

Drug	Dose Regimen	Cost per cycle (£)	Cost per course (£)
Azacitidine	**75mg/m^2 subcutaneously daily for 7 days every 28 days**	**4,494**	**26,964**
Cytarabine	20mg/m^2 subcutaneously daily for 14 days every 28 days	55	218
Cytarabine	100 to 200mg/m^2 by continuous intravenous infusion daily for 7 days		
plus daunorubicin or plus idarubicin or plus mitoxantrone	45 to 60mg/m^2 intravenously daily for 3 days 9 to 12mg/m^2 intravenously daily for 3 days 8 to 12mg/m^2 intravenously daily for 3 days	715 to 1,099 841 to 1158 355 to 409	

Doses are for general comparison and do not imply therapeutic equivalence. Costs for azacitidine from MIMS June 2011, for idarubicin from eVadis 10 June 2011 and for cytarabine, daunorubicin and mitoxantrone from British National Formulary 61 March 2011. Costs for azacitidine assume the use of two 100mg vials of azacitidine per day which would be necessary for patients with body surface areas of $1.8m^2$. The cost per course is for the minimum recommended six cycles for azacitidine and four cycles for low dose cytarabine but may be longer in some patients. The costs for intensive chemotherapy are calculated for one cycle only.

Additional information: budget impact

The company estimated the population eligible for treatment to be 67 patients in year 1 falling to 31 by year 5. In year 1 prevalent patients would be eligible for treatment, whereas in subsequent years incident patients would be eligible for treatment. Based on an estimated uptake of 20% in year 1 and 40% in year 5, the impact on the medicines budget was estimated at £490k in year 1 and £517k in year 5. The net medicines budget impact was estimated at £180k and £243k in years 1 and 5 respectively. These figures do not take account of the discount offered by the patient access scheme.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

Fenaux P, Mufti GJ, Hellstrom-Lindberg E *et al.* Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol* 2009;10:223-232.

Garcia-Manero G. Improving survival in myelodysplastic syndromes. Editorial. Lancet Oncol 2009;10:200-201

European Medicines Agency (EMA). European public assessment report (EPAR) for azacitidine (Vidaza®). www.ema.europa.eu

This assessment is based on data submitted by the applicant company up to and including 18 July 2011.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in

determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.