



24 November 2010

Jeremy Powell  
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Dear Mr Powell,

**Azacitidine for the treatment of myelodysplastic syndromes (MDS), chronic myelomonocytic leukaemia (CMML) and acute myeloid leukaemia (AML) – Appraisal Consultation Document #3**

Celgene is grateful for the opportunity to comment on the ACD. We have structured a response based on the new key issues featured in this document.



**A summary of the key points that have been addressed by Celgene**

We have focussed primarily on new observations and decisions made by the Appraisal Committee since the FAD was published in March 2010:

- Application of end of life criteria
- Approach to comparators
- Sensitivity analyses relating to “blended” approach



Our detailed responses follow on the next pages.

## **ACD section 4.8 - Clinical Effectiveness**

Celgene agree with the summarisation of the clinical evidence and remain pleased that the Committee recognises the clinical value of azacitidine.

## **ACD section 4.23 - End of Life Criteria**

Celgene agrees with the Committee's determination that azacitidine within this appraisal fulfils the criteria for consideration as a life-extending, end-of-life treatment. Importantly, we note that this determination has been made in the context of azacitidine's comparison with all conventional care types combined (i.e. a 'blended' comparison).

## **ACD Section 4.19 - Approach to comparators**

### **Identification of Subgroups**

The pivotal azacitidine clinical trial, AZA-001, allows the calculation of incremental cost-effectiveness ratios (ICERs) within the pre-selected subgroups set out in the AZA-001 trial. The subgroups are as follows:

- Pre-selected for supportive care (BSC)
- Pre-selected for supportive care plus low-dose chemotherapy (LDC)
- Pre-selected for supportive care plus standard dose chemotherapy (SDC)

Until the last Appraisal Committee meeting, Celgene and NICE had been working with cost-effectiveness comparisons of azacitidine to "conventional care" in each of these three subgroups.

After further consideration, including the investigation of further evidence submitted by Celgene, the Appraisal Committee has concluded that it cannot make evidence-based recommendations based on the ICERs calculated in each subgroup, because there is insufficient robust evidence to allow the subgroups to be identified in clinical terms for NICE guidance.

Given the Appraisal Committee's conclusions in this regard, it was determined in the ACD that the most appropriate ICER for the appraisal of azacitidine would be obtained by the use of a weighted average of incremental costs and QALYs estimated for each of the pre-specified subgroup comparisons. Celgene would agree that this approach follows logically from the Committee's conclusions with regard to subgroups.

### **Alternative approaches**

The DSU asserted that the ideal way of assessing azacitidine's cost effectiveness would be an incremental analysis involving each of the treatment options ordered according to their level of benefit. Thus, incremental costs and QALYs would be calculated for:

- LDC versus BSC
- Azacitidine versus LDC

However, the Appraisal Committee and DSU acknowledged that it would be difficult to adjust such an analysis for the fact that patients who are eligible for BSC, LDC and SDC are often likely have substantially different clinical profiles. Eligibility for each of the three conventional care options is not entirely mutually exclusive – patient and clinician preference are known to play a role – but an incremental approach which fails to account for patient

differences would carry little meaning and we noted that this observation was made during the Appraisal Committee meeting.

For this reason, and because of the Committee’s stated position with regard to the identification of subgroups, the weighted average approach was taken instead. However, some of the concerns which were raised regarding a fully incremental approach have been maintained, as described on the following page.

**Adjustment to weighted average ICER**

The weighted average ICER analysis presented by Celgene gave a value of £56,945/QALY gained. The Celgene ICER weighted incremental costs and QALYs for BSC, LDC and SDC subgroup analyses according to the proportions of patients pre-allocated to BSC, LDC and SDC in the AZA-001 trial. Clinical experts attending NICE Appraisal Committee hearings as well as written evidence statements collected during this appraisal have confirmed that the allocation of patients to subgroups in AZA-001 trial reflects current UK clinical practice.

Celgene’s evidence submission prior to this ACD provided real-life clinical data from the Haematological Malignancies Research Network (HMRN) patient registry. This registry captures current usage of BSC, LDC and SDC in UK clinical practice for MDS patients although not specifically in the population falling under the azacitidine marketing authorisation (HMRN registry includes data from all MDS patients).

The Appraisal Committee carried out an adjustment to the weighted average ICER, using treatment allocation proportions observed in HMRN registry. The ACD states that the proportions (69% for BSC, 13% for LDC and 18% for SDC) are sourced from the Int-2/high-risk subgroup in the HMRN registry, but this seems at odds with the data in the HMRN report as well as in the DSU addendum to the Assessment Report. It would appear that the Committee actually used treatment allocations seen in the subgroup of MDS patients with the RAEB disease subtype – a subset of the azacitidine license (approx. 58% of the AZA-001 population). For clarity, we have presented the weighting alternatives together with corrected percentages and recalculated ICERs in Table 1.

**Table 1. Weighted average ICERs based on treatment allocations in AZA-001 and HMRN registry**

Source for treatment allocation proportions	Proportion receiving...			Resulting ICER (£/QALY gained)
	(calculation supplied below)			
	BSC	LDC	SDC	
<b>AZA-001 trial</b> Provided by Celgene N=179†	58.66% (105/179)	27.37% 49/179	13.97% 25/179	56,991
<b>HMRN registry</b> MDS patients classified as Int-2 or high risk  N=123 (3 patients who died have been excluded)	59.35% (73/123‡)	12.20% (15/123)	28.46% (35/123)	57,860
<b>HMRN registry</b> MDS patients with RAEB disease sub-type  N=259	68.73% (178/259‡)	13.13% (34/259)	18.15% (47/259)	58,847

NOTES: All estimates include the 7% discount patient access scheme and assumptions applied in the ACD; † we identified a rounding error in treatment allocation percentages from AZA-001 as presented in the last submission; this has been corrected along with the ICER in the table above; ‡ BSC includes ‘observation only’ from HMRN registry.

The Appraisal Committee has stated that it considers the most plausible ICER to be one which is based on the treatment allocations seen in the HMRN registry for MDS Int-2/high-risk patients. If we understand correctly, preference is given to these weightings over those available in AZA-001 for two reasons:

1. *The Committee considers that the HMRN registry may provide a more representative picture of current UK clinical practice than the AZA-001 trial.*
2. *The Committee considers that the weighted average ICER provided by Celgene may be an underestimate due to the inclusion of incremental costs and benefits of azacitidine versus LDC.* Since LDC is likely to be cost-ineffective compared to BSC it was felt that an element of double counting is introduced by involving a comparison of azacitidine against a therapy (LDC) which the Institute would probably not recommend as a cost-effective use of NHS resources. The adjustment carried out in Table 1 was also considered an appropriate way of increasing the ICER to account for this consideration.

We would like to comment on this approach briefly. We feel that the adjustments carried out in Table 1 form a useful sensitivity analysis for the weighted average approach. However, we do not believe that the adjustments are a sound basis for the calculation of a 'preferred' ICER, especially given the Committee's stated objectives in applying these adjustments. Our comments against each of the Committee's stated objectives are set out below:

1. *The Committee considers that the HMRN registry may provide a more representative picture of current UK clinical practice than the AZA-001 trial.* The HMRN registry provides current insight into which treatments MDS patients are receiving. In principle, we consider the adjustments in Table 1 to be a useful sensitivity analysis. However, the HMRN registry captures information in all MDS patients, not just those indicated in the azacitidine license. This introduces uncertainty as to whether the adjustments provide a more realistic ICER for the UK than would be obtained by using the AZA-001 data. The Committee has attempted to address this uncertainty by applying treatment proportions seen in Int-2/high-risk or RAEB subsets only; both of these subsets are part of the azacitidine license and around 88% of patients in the AZA-001 trial were classified as Int-2/high-risk. But this adjustment does not control for the other clinical characteristics on which the HMRN registry patients may differ substantially from those in the azacitidine license. The most important of these are shown below:
  - a. Transfusion requirements at time of treatment allocation
  - b. Age and ECOG status
  - c. Cytogenetic profile
  - d. Eligibility for stem cell transplantation (azacitidine license explicitly rules out transplant-eligible patients)
  - e. Number of cytopenias

All of these characteristics have the potential to influence treatment allocation. Stem cell transplantation eligibility is of particular concern. The HMRN data suggest that 28.5% of Int-2/high-risk patients received intensive chemotherapy or SDC, a finding which goes against expert testimony heard in earlier Appraisal Committee meetings and the Appeal hearing. Over the course of this appraisal, experts have generally

indicated that SDC is rarely given in azacitidine-licensed patients; this treatment tends rather to be reserved for patients being prepared to undergo stem cell transplantation.

For these reasons we cannot agree with the Committee that its adjustment to the ICER provides a more accurate reflection of UK clinical practice than the data from AZA-001.

2. ***The Committee considers that the weighted average ICER provided by Celgene may be an underestimate due to the inclusion of incremental costs and benefits of azacitidine versus LDC.*** The adjustment to the ICER is felt to partially compensate for a modelling issue which is often important when evaluating the cost-effectiveness of multiple therapies relative to one another. We cannot accept the link drawn in the ACD between this modelling issue and the adjustment in Table 1 for two reasons:
  - a. We disagree in principle with the notion that the conventional care regimens need to be considered together with azacitidine in an incremental analysis. We believe that the Committee's concerns about the cost-ineffective increment between LDC and BSC are not relevant to this appraisal. This is a single technology appraisal of azacitidine versus conventional care. LDC, SDC and BSC are all part of the conventional care regimen for MDS and decisions as to whether a patient will be treated with LDC or BSC are not subject to cost-effectiveness evaluation in clinical practice – the relative difference in budget impact is small (£2,000 over a lifetime). The way in which conventional care options are used and assigned has been observed to vary in surveys carried out by Celgene, and patient preference plays a role. This is why the patients in AZA-001 were pre-allocated to BSC, LDC and SDC and thereafter effectively considered as subgroups of a main comparison of azacitidine to “conventional care regimens”.
  - b. If the Committee's concern about the cost-ineffectiveness of LDC compared to BSC is to be taken on board, an adjustment based on parameters which are unrelated to this concern seems arbitrary and inaccurate.





**Table 2. Weighted average ICERs applying revised patient access scheme**

Source for treatment allocation proportions	Weighted Average ICER (£/QALY gained)
<b>AZA-001 trial</b> Provided by Celgene	49,405
<b>HMRN registry</b> MDS patients classified as Int-2 or high risk	49,837
<b>HMRN registry</b> MDS patients with RAEB disease sub-type	50,920



Jeremy, should you or your team have any further questions in relation to this response, please do not hesitate to contact me.

Kind Regards,

Carl Gibbons  
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Celgene UK and Ireland