MYELODYSPLASTIC SYNDROMES - AZACITIDINE: REVIEW OF CELGENE'S RESPONSE TO THE POST-APPEAL ACD

REPORT BY THE DECISION SUPPORT UNIT

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EXECUTIVE SUMMARY

In response to the consultation on the second Appraisal Consultation Document (ACD) for azacitidine for the myelodysplastic syndromes, chronic myelomonocytic leukaemia, and acute myeloid leukaemia, the manufacturer, Celgene, submitted new cost effectiveness analyses including a revised patient access scheme (PAS), and comments on the approach and assumptions used by the Committee in formulating its preliminary recommendations. The DSU was asked to review the revised cost-effectiveness estimates and provide an independent view on the concerns raised by Celgene.

The DSU was able to validate the revised cost-effectiveness estimates submitted by Celgene. The DSU has confirmed that the changes to the PAS have been implemented correctly in the modelling and that the weighted ICERs reported follow from the proportions of patients receiving low dose chemotherapy (LDC), standard dose chemotherapy (SDC) and best supportive care (BSC) presented by the manufacturer.

Celgene raised concerns regarding use of the Haematological Malignancy Research Network (HMRN) registry population to determine the proportions receiving each of the conventional care regimens in UK current practice. In particular they were concerned that patients receiving SDC prior to stem cell transplant would be included in the HMRN registry but would not be eligible to receive azacitidine under its licensed indication. The DSU conducted sensitivity analyses to examine the extent to which the weighted average ICER is sensitive to the proportion receiving SDC. Reducing the proportion receiving SDC in the weighted average to either the rate used in the AZA-001 trial, or to zero, had the effect of increasing the ICER.

Celgene also raised concerns regarding the Committee's consideration of the weighted average ICER in the ACD. The Committee noted in the ACD that because of the inclusion of a potentially cost-ineffective technology (that is, low-dose chemotherapy) in the weighted average, the true ICER of azacitidine compared with usual care was probably higher than the estimate provided by the weighted ICER. Celgene has argued that the Committee's concerns about the potential cost-ineffective increment between LDC and BSC are not relevant to this appraisal and that the ICER should not be adjusted to account for this factor. This report concludes that the preferred methodological approach would be to conduct a full incremental

comparison of all conventional care regimens (BSC, LDC, and SDC) to ensure that azacitidine is being compared with the most cost-effective alternative intervention, and that separate incremental analyses should be conducted for the subgroups selected to receive different conventional care regimens in the trial, as these are considered to represent heterogeneous populations. The fact that it is not possible to perform an incremental analysis of all potential comparator regimens (BSC, LDC, and SDC) across all the subgroups which make up the azacitidine indicated population, adds uncertainty to the estimates of cost-effectiveness generated by the weighted average approach. However, in the absence of robust evidence on which to base a full incremental analysis of the conventional care regimens, it is not possible to be certain of the direction or size of any potential bias. However, the DSU considers that the ICERs calculated using the weighted average approach should be treated with caution if cost-effectiveness has not been demonstrated within each subgroup of the indicated population, as even if the weighted average ICER is considered to be acceptable, it is not certain that an acceptable level of cost-effectiveness would be achieved within each of the heterogeneous subgroups.

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ABBREVIATIONS AND DEFINITIONS

ACD	Appraisal Consultation Document
AML	Acute myelogenous leukemia
AZA	Azacitidine
BSC	Best supportive care
CCR	Conventional care regimen
CMML	Chronic myelomonocytic leukemia
DoH	Department of Health
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
HMRN	Haematological Malignancy Research Network
ICER	Incremental cost-effectiveness ratio
FAD	Final Appraisal Determination
LDC	Low dose chemotherapy
SDC	Standard dose chemotherapy
MDS	Myelodysplastic syndromes
PAS	Patient access scheme
PASLU	Patient Access Scheme Liaison Unit
PSA	Probabilistic Sensitivity Analysis
QALY	Quality adjusted life year
RAEB	Refractory anaemia with excess blasts

1. INTRODUCTION

1.1. BACKGROUND

In response to the consultation on the second Appraisal Consultation Document (ACD) for azacitidine for the myelodysplastic syndromes, chronic myelomonocytic leukaemia, and acute myeloid leukaemia, the manufacturer, Celgene, submitted new cost effectiveness analyses including a revised patient access scheme (PAS), and comments on the approach and assumptions used by the Committee in formulating its preliminary recommendations.

Aims and objectives of the DSU review

1. To review the new cost effectiveness estimates submitted by Celgene in November 2010 and determine the following;
    a) Have the described changes to the PAS been implemented correctly in the modelling?
    b) Have the proportions of patients in the different conventional care regimen (CCR) arms been implemented correctly in the updated cost effectiveness analyses?

2. To provide an independent view on the following concerns raised by Celgene regarding the assumptions made by the Committee in formulating its preliminary recommendations
    a) That the Committee's consideration that the weighted average incremental cost-effectiveness ratio (ICER) provided by Celgene may be an underestimate, due to the inclusion of a potentially cost ineffective comparator in the assessment, is not appropriate.
    b) That the use of the Haematological Malignancy Research Network (HMRN) registry population to determine the proportions receiving each of the comparator regimens in UK current practice is not appropriate.

2. REVIEW OF THE REVISED COST-EFFECTIVENESS ESTIMATES

The manufacturer's response to the post-appeal ACD included two tables of ICERs, one using the original PAS and a second using a revised PAS, which was still under consideration by the Department of Health (DoH) and NICE's Patient Access Scheme Liaison Unit (PASLU) at the time this report was completed. The previous PAS offered by Celgene and accepted by the DoH involved a 7% discount to the drug acquisition cost. [redacted]

2.1. COST-EFFECTIVENESS WHEN USING THE ORIGINAL PAS

In Table 1 of their response to the ACD, the manufacturer presents cost-effectiveness estimates when using three different sets of proportions to generate a weighted ICER across the three conventional care regimens (CCRs). The three different set of proportions considered represent alternative estimates from the AZA-001 trial and the HMRN registry. The DSU was able to replicate both the proportions and the ICERs cited in Table 1 of Celgene's response to the ACD.

For the analysis using the proportions from the RAEB subgroup of the HMRN registry, the difference between the manufacturer's ICER of £58,847 per QALY and the DSU's previously reported ICER of £58,900 (Davis 2010) is due to rounding in the proportions used by the DSU to the nearest 0.1%. The DSU also noted that the manufacturer has corrected the method used to generate the weightings from the AZA-001 trial. In their previous submission, Celgene applied the individual weightings from each arm, which created a potential for bias due to slightly different distributions of pre-selected best supportive care (BSC), low dose chemotherapy (LDC) and standard dose chemotherapy (SDC). The ICERs in the AZA-001 row of Table 1 correctly use the same proportions to weight both arms. However, this proportion is taken from the CCR arm of the AZA-001 trial. As the allocation to azacitidine (AZA) or CCR arm occurred after allocation to the pre-selected CCR, the most generalisable estimate of the likely use of CCR from the AZA-001 trial comes from using the pre-randomisation allocation across both arms. This gives slightly different proportions, of 62%, 26% and 12% for BSC, LDC and SDC respectively (see Table 1). Using these

proportions the weighted ICER is £57,400 from the AZA-001 trial which is marginally higher than the manufacturer's estimate, as shown in Table 1.

As the manufacturer's estimates were based solely on the deterministic model, the DSU has calculated weighted ICERs using the mean costs and QALYs from 10,000 probabilistic samples. It can be seen, in Table 2, that the mean ICERs generated by the probabilistic sensitivity analysis (PSA) are lower than those generated by the deterministic model. (The reason for this discrepancy is not immediately obvious and the DSU was unable to investigate the cause within the timeframe available). It should be noted that there was considerable uncertainty in the ICER estimates such that even for the most favorable ICER in Table 2, 1% of PSA estimates had an ICER under £30,000 per QALY, 62% had an ICER under £60,000 per QALY and 82% had an ICER under £90,000 per QALY.

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

Source for treatment allocation proportions	Proportion receiving each of the conventional care regimens			Resulting ICER using deterministic model (£/QALY gained)	Resulting ICER using probabilistic model (£/QALY gained)
	BSC	LDC	SDC		
AZA-001 trial N=179 (proportion across CCR arm)	58.66% (105/179)	27.37% 49/179	13.97% 25/179	56,991	54,818
AZA-001 trial† N=358 (proportion across both arms)	62.01% (222/358)	26.26% (94/358)	11.73% (42/358)	57,403	55,282
HMRN registry 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	55,031
HMRN registry MDS patients with RAEB disease sub-type N=259	68.73% (178/259‡)	13.13% (34/259)	18.15% (47/259)	58,847	56,338

† Additional scenario undertaken by DSU

2.2. COST-EFFECTIVENESS WHEN USING THE REVISED PAS

The DSU was able to replicate the ICERs reported by the manufacturer in Table 2 by using revised cost and QALY estimates generated by replacing the original PAS scheme applied in the previous model with the revised PAS scheme proposed in confidence by the manufacturer and applying the proportions cited in Table 1. Adjusting the proportions used to represent the distribution in the AZA-001 trial to use the pre-randomisation distribution across both arms,

as described above, increased the ICER marginally to £49,800 per QALY as shown in Table 2.

As the manufacturer's estimates were based solely on the deterministic model, the DSU has also calculated weighted ICERs using the mean costs and QALYs from 10,000 PSA samples. It can be seen, in Table 2, that the mean ICERs generated by the PSA are lower than those generated by the deterministic model. Again, it should be noted that there was considerable uncertainty in the ICER estimates such that even for the most favorable ICER in Table 2, 6% of PSA estimates had an ICER under £30,000 per QALY, 71% had an ICER under £60,000 per QALY and 84% had an ICER under £90,000 per QALY. The costs and QALY estimates for each subgroup which have been used to calculate the weighted average ICERs in Table 2 are provided in the Appendix for reference.

Table 2. Weighted average ICERs applying revised PAS

Source for treatment allocation proportions	Weighted Average ICER using deterministic model (£/QALY gained)	Weighted Average ICER using probabilistic model (£/QALY gained)
AZA-001 trial (proportion from CCR arm)	49,405	47,336
AZA-001 trial (proportion across both arms)†	49,808	47,782
HMRN registry MDS patients classified as Int-2 or high risk	49,837	47,224
HMRN registry MDS patients with RAEB disease sub-type	50,920	48,581

†Additional scenario undertaken by DSU

2.3. SUMMARY

The DSU was able to validate the revised cost-effectiveness estimates and confirm that the changes to the PAS have been implemented correctly in the modelling and that the weighted ICERs reported follow from the proportions of patients receiving LDC, SDC and BSC presented by the manufacturer. The DSU has also provided an alternative estimate using the proportions across the whole AZA-001 trial rather than the proportions specifically from the CCR arm. The DSU has also provided the mean ICER estimates derived from the probabilistic analysis which were marginally lower than the deterministic ICERs reported by the manufacturer.

3. CONCERNS REGARDING THE INCLUSION OF A POTENTIALLY COST-INEFFECTIVE COMPARATOR

Celgene has expressed concern regarding the fact that the Committee considered 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" (Celgene 2010). They argue that the Committee's concerns about the potential cost-ineffective increment between LDC and BSC are not relevant to this appraisal and that the ICER should not be adjusted to account for this factor. The DSU believes that there are two methodological issues that need to be considered by the Committee when making their response to Celgene's concerns. The first is the methodological limitations of using a weighted average to estimate and ICER across subgroups which are believed to have differing clinical characteristics and therefore potentially differing cost-effectiveness. The second issue is the present uncertainty regarding the cost-effectiveness of LDC relative to BSC and how this relates to uncertainty in the weighted ICER.

3.1. USE OF A WEIGHTED AVERAGE TO CALCULATE COST-EFFECTIVENESS ACROSS HETEROGENEOUS SUBGROUP

There will inevitably be some variation in the cost-effectiveness of using a particular intervention across a population. Where this variation can be explained by known differences between patients it is described as heterogeneity. Where possible, sources of heterogeneity in cost-effectiveness analysis should be explored, as appropriately reflecting subgroups and heterogeneity in decisions has the potential to increase population health gains by allowing interventions to be targeted at those subgroups in which they are cost-effective (Sculpher 2008). The alternative approach, of calculating the average cost-effectiveness across a heterogeneous population, will have a cost in terms of net monetary or health benefit, unless it has been demonstrated that the intervention is cost-effective within each subgroup. However, where it is not possible in practice to make recommendations for a specific subgroup, it may be necessary to consider the average cost-effectiveness across the population as a whole, whilst accepting that this may fail to optimise population health gains.

In the AZA-001 trial patients were pre-selected to receive one of the three conventional care regimens (CCRs) prior to randomisation to either CCR or AZA. The method used by the investigator to determine the preselected CCR is described in the main study publication "as

clinical judgment on the basis of age, ECOG performance status, and comorbidities". (Fenaux 2009) In the manufacturer's original submission the basis for selection is described as "age, general condition, co-morbidities and patient preference". Therefore, it is likely that the characteristics of patients will differ between the three trial subgroups. In support of this, it is stated in the manufacturer submission that patients in the subgroup selected to receive standard-dose chemotherapy were younger and had better ECOG performance status and higher-risk disease. (Celgene 2009) It is also therefore likely that the cost-effectiveness of both AZA and the CCRs will vary between these patient subgroups and ideally one would want to identify the most cost-effective intervention for each patient subgroup and make separate recommendations for each subgroup accordingly.

However, due to the use of clinical judgment and patient preference to determine allocation to the pre-selected CCR, it is not possible to identify a consistent set of characteristics that differentiate exactly between those patients who were preselected to receive BSC and those who were preselected to receive LDC or SDC. Furthermore, the Committee has been presented with evidence from the manufacturer and testimony from clinical experts which supports the view that there isn't a clear set of criteria used in the UK to determine which patients are eligible for either LDC or SDC (Nice 2010). It is therefore difficult to identify specific subgroups of patients from within the azacitidine indicated population who can be expected to be similar to the patients pre-selected to receive BSC, LDC or SDC within the AZA-001 trial, and for whom separate recommendations could be made based on cost-effectiveness estimates that are specific to that subgroup.

In the absence of a clear set of criteria that could be used to differentiate between these different patient subgroups, the Committee considered that it would be reasonable to calculate the cost-effectiveness of AZA compared to usual care, using the mean costs and QALYs across the whole AZA indicated population by taking a weighted average of the costs and QALYs across the patient subgroups. However, as discussed above, this approach may fail to make best use of NHS resources if azacitidine is in fact cost-effective in one subgroup, but not cost-effective in another subgroup (Sculpher 2008). If the ICER for azacitidine vs usual care in the population pre-selected to receive BSC is considered by the Committee to be too high to represent a cost-effective use of NHS resources in this subgroup, then it is reasonable for the Committee to consider the ICER calculated using the weighted average with caution.

3.2. IMPACT OF UNCERTAINTY REGARDING RELATIVE COST-EFFECTIVENESS OF LDC AND BSC

When comparing AZA to usual care it is important to ensure that the appropriate "usual care" comparator is selected. The NICE methods guide describes the selection of appropriate comparators, stating that consideration should be given to "routine and best practice in the NHS" (NICE 2008). As stated in previous DSU reports (Longworth 2008, Davis 2010), the DSU considers that if there is more than one intervention which could be considered to represent either routine or best practice care, then an incremental analysis should be conducted to establish the most cost-effective comparator and the intervention being appraised should be compared to this treatment. Furthermore, where it is possible to specify subgroups with identifiable characteristics, for which either the comparator interventions differ or for which the cost-effectiveness is expected to differ, it would be appropriate to conduct an incremental analysis within each subgroup.

In the case of this appraisal, whilst it may not be possible to make separate recommendations for each subgroup, the aim should still be to compare AZA to the most cost-effective comparator within each patient subgroup, as this represents "best practice" in the absence of AZA being available. Therefore, what is required is a comparison of BSC, LDC and SDC for each subgroup. Then "best practice" can be identified for that subgroup and the incremental costs and QALYs of AZA can be calculated relative to "best practice", which may be a different CCR for each subgroup. These incremental costs and QALYs could then be used in the weighted average to calculate the cost-effectiveness of AZA compared to usual care in the whole AZA indicated population.

Particular conventional care regimens could potentially be excluded from the incremental analysis if they are definitely not a potential option for a particular subgroup. However, given the current lack of consensus on criteria for determining whether BSC, LDC or SDC is considered appropriate, it is difficult to specify subgroups in which particular conventional care options can definitely be excluded. This is supported by the fact that some degree of physician and / or patient preference was used to determine allocation to the CCRs in the AZA-001 trial. Therefore, the preferred approach would be full incremental comparison for each subgroup to ensure that AZA is being compared with the most cost-effective alternative intervention.

However, the evidence we have available from the AZA-001 trial is limited in that we only have evidence on AZA compared to one of the CCRs for each of the patient subgroups. If we believe the subgroups to be heterogeneous, we cannot infer what the expected costs and QALYs would be if one of the CCRs had been used in a different population subgroup. For example, we cannot say what the costs and QALYs would have been if LDC had been used in those patients pre-selected to receive BSC. Nor can we say for definite what the outcome would have been if BSC had been used in those patients pre-selected to receive LDC. Therefore a full incremental analysis of all the conventional care regimens is not possible, given the evidence available.

What we can say is that calculating the weighted ICER using the incremental costs and QALYs of AZA compared to only one comparator for each subgroup, effectively assumes that each subgroup received the optimal (most cost-effective) CCR in the trial. In the absence of a robust assessment of the cost-effectiveness of the different comparators comprising usual care, it is not possible to robustly quantify either the direction or size of any potential bias introduced by this assumption.

3.3. SUMMARY

In conclusion, using a weighted average approach to estimate the cost-effectiveness of azacitidine compared to usual care may lead to azacitidine being recommended in some patients for whom it is not cost-effective, as the average cost-effectiveness is being calculated across heterogeneous subgroups of the population. Therefore, the ICERs calculated using this approach should be treated with caution if cost-effectiveness has not been demonstrated within each population subgroup. As even if the weighted average ICER is considered to be acceptable, it is not certain that an acceptable level of cost-effectiveness would be achieved within each subgroup. In addition to this, the fact that it is not possible to perform an incremental analysis of all potential comparator regimens (BSC, LDC, and SDC) across all the subgroups which make up the azacitidine indicated population, adds further uncertainty to the estimates of cost-effectiveness generated by the weighted average approach, as it is unclear whether the conventional care regimen used in each of the trial subgroups represents the most cost-effective option for that subgroup.

4. USE OF THE HMRN REGISTRY POPULATION TO ESTIMATE CURRENT UK PRACTICE PATTERNS

The manufacturer has expressed concern regarding the fact that the HMNR registry is not restricted to patients who would be eligible to receive azacitidine and therefore may not be adequately representative of the azacitidine indicated population (Celgene 2010). They suggest that the following factors may vary between the registry population and the azacitidine indicated population:

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

The manufacturer has expressed particular concern regarding the proportion of patients receiving SDC within the HMRN registry which they argue is usually reserved for patients preparing to undergo stem cell transplant. For these reasons, they argue that the distribution of comparator regimens seen in the trial is more representative of the mix of comparators used in the azacitidine indicated population than the distributions based on either the IPSS intermediate-2/high risk subset or the WHO RAEB subset of the HMRN registry.

The information available to the Committee on the HMRN registry patients is limited to that provided in the manufacturer's post appeal submission. It is not possible to extract from the information provided a subset of patients which matches the azacitidine indicated population exactly. Nor is it possible to adjust for all of the factors listed above that the manufacturer states may differ. However, as there was particular concern expressed regarding the proportion receiving SDC, the DSU wished to explore whether the cost-effectiveness estimates are sensitive to uncertainty regarding this proportion.

4.1. SENSITIVITY ANALYSIS ON THE PROPORTION RECEIVING SDC IN CURRENT CLINICAL PRACTICE

As no data is available on the proportion of those receiving SDC in the HMRN registry who receive it prior to stem-cell transplant, rather than as an alternative to BSC or LDC, it is difficult to say exactly how much the inclusion of these patients in the calculation of the

weighted average ICER may have biased the cost-effectiveness estimate. The DSU has conducted two sensitivity analyses to explore the extent of the possible bias. In the first sensitivity analysis, all patients receiving SDC in the HMRN registry were removed from the weighted average used to calculate the ICER across the whole azacitidine indicated population. This effectively assumes that SDC is only used prior to stem cell transplant in the UK. In the second sensitivity analysis, the proportion receiving SDC was taken from the AZA-001 trial and then the split between BSC and LDC was taken from the HMRN registry. The proportions applied and resultant weighted ICERs are given in Table 3. ICERs are reported for both the original PAS and the revised PAS. Reducing the proportion receiving SDC in the weighted average to either the rate used in the AZA-001 trial, or to zero, increased the ICER in all cases.

Table 3 Sensitivity analyses exploring reduced SDC usage (deterministic estimates)

Source for treatment allocation proportions	**Proportion receiving each of the conventional care regimens**			**ICER with original PAS (£/QALY gained)**	**ICER with revised PAS (£/QALY gained)**
	BSC	**LDC**	**SDC**		
Sensitivity analysis assuming zero use of SDC in the azacitidine eligible population					
AZA-001 trial N=358 (proportion across both arms)	70.25%	29.75%	-	58,087	50,639
HMRN registry MDS patients classified as Int-2 or high risk N=123 (3 patients who died have been excluded)	82.95%	17.05%	-	60,145	52,432
HMRN registry MDS patients with RAEB disease sub-type N=259	83.96%	16.04%	-	60,316	52,580
Sensitivity analysis applying proportion receiving SDC from AZA-001 trial and split between LDC and BSC from HMRN registry					
HMRN registry MDS patients classified as Int-2 or high risk N=123 (3 patients who died have been excluded)	73.22%	15.05%	11.73%	59,224	51,386
HMRN registry MDS patients with RAEB disease sub-type N=259	74.11%	14.06%	11.73%	59,374	51,516

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APPENDIX

Table 4A1 Base-case results* for each pre-selected subgroup when using the revised PAS

Treatment option	*Deterministic estimates*					*Probabilistic estimates*		
	Costs incurred, £	*QALYs gained*	*Incremental costs, £*	*Incremental QALYs*	*ICER, £*	*Incremental costs, £*	*Incremental QALYs*	*ICER, £*
Pre-selected for BSC								
Azacitidine	83,573	2.04	55,576	1.01	55,071	53,492	1.01	53,023
BSC	27,998	1.03						
Pre-selected for LDC								
Azacitidine	92,947	2.44	57,263	1.34	42,752	54,076	1.30	41,463
LDC	35,684	1.10						
Pre-selected for SDC								
Azacitidine	83,274	1.91	39,214	0.93	42,334	35,341	0.94	37,655
SDC	44,060	0.98						

* Weibull curve fit to survival data, no vial sharing and the revised PAS