National Institute for Health and Clinical Excellence

MidCity Place
71 High Holborn
London
WC1V 6NA

Tel: 0845 003 7780
Fax: 0845 003 7785

Email: nice@nice.org.uk
www.nice.org.uk

Ms Aoife Kilkenny
Associate Director
External Affairs and Market Access
Celgene Ltd
Morgan House
Madeira Walk
Windsor
Berkshire
SL4 1PE

18 November 2009

Dear Ms Kilkenny,

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

Recent reviews by both the Evidence Review Group and the Decision Support Unit have identified errors in the economic model submitted with your clarified response to the ACD (latest version dated 21 Oct 2009). These errors relate to the way in which the survival analyses are incorporated into the model, and are described below. As a result of these errors, we have rescheduled the Committee discussion to 7 January 2010.

We request you to provide a written response and a corrected version of the economic model to the Institute by **17:00**, **30 November 2009.**

If you present data that are not already referenced in the main body of your submission and that data are seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

If you have further queries on the technical issues raised in this letter, please contact Whitney Miller (Whitney.Miller@nice.org.uk). Procedural questions should be addressed to Jeremy Powell (Jeremy.Powell@nice.org.uk) in the first instance.

Regards

Dr Elisabeth George
Associate Director - Appraisals
Attached: checklist for in confidence information

Points for Correction

1. The log-normal parameters (μ,σ) in the model are identical for both the BSC and LDC CCR sub-groups, despite the fact that observed survival between the two groups differs. The same is true for the Gompertz survival functions. In effect, the model calculates survival curves for the BSC and LDC CCR sub-groups using a common parameter set when the log-normal and Gompertz survival functions are chosen.

Please correct this or provide justification for the use of common parameter sets.

2. Errors in the calculation of transitional probabilities affect both the deterministic and probabilistic analyses:

a. Calculations of the transitional probabilities contain errors for the exponential, lognormal and Gompertz functional forms (columns M-0 in each of the "Flow" sheets). These errors result in an illogical probability for the final cycle (Row 278). It is suspected that the relevant probability is being calculated by looking forward one cycle, rather than looking back. As a result, no legitimate estimates exist for the final cycle.

Please correct this.

b. Sampling errors occur within the probabilistic sensitivity analyses. As currently programmed, the model does not produce estimates of mean cost and effect for all simulations in the PSA. This can be seen in two ways.

i. In the model options, select Weibull for the survival curve for all treatments. Run a new PSA. You will note that in the PSA output sheets, there are numerous simulations that do not yield results. The relevant cells return error messages (#div/0!).

ii. Turn the PSA option on in the model controls (option 1c) and look at the transition probabilities in the flow sheets (e.g., AZA SDC flow sheet, columns K to 0, rows 278 upwards). Pressing f9 to sample values will show that some samples yield errors in the calculated probabilities once the probability reaches 1. This is apparent for several of the possible survival functions.

Please correct this.

***3.** Please provide an explanation for why the ICERs generated by the model do not match those in the written response to clarification (for all LDC pre-selected subgroups and the SDC pre-selected subgroup in Table 1.1; response dated 7 Oct 2009).*

4. *Please demonstrate that the results of the deterministic and probabilistic analyses agree with one another, noting the number of Monte Carlo simulations required.*

Where these results differ from those included in your previous response to clarification (dated 7 Oct 2009), please resubmit a full tabulation of the results.