THE CLINICAL- AND COST-EFFECTIVENESS OF LENALIDOMIDE FOR MULTIPLE MYELOMA IN PEOPLE WHO HAVE RECEIVED AT LEAST ONE PRIOR THERAPY: AN EVIDENCE REVIEW OF THE SUBMISSION FROM CELGENE

Addendum to the report submitted on 1st September 2008

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This addendum is in response to the response from Celgene (received November 2008) on our (the ERG) report.

In their response, Celgene present results from their adjusted cost-effectiveness model for patients in the >1 prior therapies subgroup only. They did not present results for patients in the 1 prior therapy subgroup.

We first respond to the results from the changes Celgene have made to their models after the ACD. Then we comment on Celgene's defence of fitting dexamethasone overall survival in their model to the median, not the mean, of the MRC data.

Celgene changes to cost-effectiveness models

We consider the results from two versions of each of their two models: the models (all patients and prior thalidomide patients) received by us on 14th August 2008 ("the adjusted August models") with the above three changes implemented by us, the ERG, and the two models received by us on 10th December 2008, the "December models" with the above three changes implemented by Celgene.

Celgene made the following three changes in the base case to both their models: the model for all patients (>1 prior therapy) and the model for patients with prior thalidomide treatment (>1 prior therapy);

1) Overall survival for Len/Dex is adjusted. In particular, in worksheet "Death 2prior the. Group", cell D18 was changed from 4.60 to 4.15.
2) A cost of £107 per outpatient visit is included.
3) Medical management costs are inflated by a factor of 1.102.

All three changes have been correctly implemented in their model.

Celgene have modelled the dose cap by limiting the cost of lenalidomide to two years for each patient. We agree with this method.

In Tables 1 and 2 below, we quote the results (a) from the adjusted August models; (b) from the December models with results quoted by Celgene; and (c) from the December models with results generated by the ERG running the model.

There are slight differences in the ICERs between the adjusted August model (with adjustments implemented by the ERG) and the December model (adjustments implemented by Celgene) (Table 1). We are unable to account for these differences.

We can replicate the ICERs quoted by Celgene when we run the December model (Table 1). Celgene did not calculate the ICERs assuming Dexamethasone overall survival fit to

the mean of the MRC data. We have calculated these ICERs using both the adjusted August model and the December model (Table 1).

For all patients (prior thalidomide + not prior thalidomide);

- The effective modelled price discount on lenalidomide is 13% (undiscounted lenalidomide cost).
- The dose cap is triggered for 17% of patients.

For the prior thalidomide subgroup;

- The effective modelled price discount on lenalidomide is 7% (undiscounted lenalidomide cost).
- The dose cap is triggered for 11% of patients.

Table 1: Comparison of results of Celgene models for >1 prior therapy all patients subgroup

		>1 prior therapy (prior thalidomide + not prior thalidomide)		
		Adjusted August model (ERG calcs)	December model (ERG calcs)	December model (Celgene calcs)
ICER (£/QALY) Dex OS fit to median MRC data	No dose cap	**35,000** (Incr. cost= £63,430, incr. QALY=1.81)	**34,200** (Incr. cost= £63,561, incr. LY=1.86)	**34,100**§
	2 year dose cap	**30,900** (Incr. cost= £56,162, incr. QALY=1.82)	**30,200** (Incr. cost= £56,170, incr. LY=1.86)	**30,300**§
ICER (£/LYG) Dex OS fit to median MRC data	No dose cap	23,500 (Incr. cost= £63,430, incr. LY=2.70)	22,900 (Incr. cost= £63,561, incr. LY=2.77)	22,900 (Incr. cost= £63,441, incr. LY=2.77)§
	2 year dose cap	20,700 (Incr. cost= £56,162, incr. LY=2.71)	£20,200 (Incr. cost= £56,170, incr. LY=2.78)	Not given
ICER (£/QALY) Dex OS fit to mean MRC data†	No dose cap	**49,400** (Incr. cost= £61,686, incr. QALY=1.25)	**49,800** (Incr. cost= £61,554, incr. QALY=1.24)	Not given
	2 year dose cap	**43,500** (Incr. cost= £54,489, incr. QALY=1.25)	**43,800** (Incr. cost= £54,291, incr. QALY=1.24)	Not given
ICER (£/LYG) Dex OS fit to mean MRC data†	No dose cap	33,700 (Incr. cost= £61,686, incr. LY=1.83)	34,000 (Incr. cost= £61,554, incr. LY=1.81)	Not given
	2 year dose cap	29,700 (Incr. cost= £54,489, incr. LY=1.84)	29,900 (Incr. cost= £54,291, incr. LY=1.81)	Not given
Mean per patient	No dose cap	£57,900	£58,100	£58,000

discounted drug (Len+Dex) cost	2 year dose cap	£50,600	£50,700	£50,800
	% reduction	13%	13%	12%
Mean per patient undiscounted drug (Len+Dex) cost	No dose cap	£60,100	£60,000	Not given
	2 year dose cap	£51,800	Model does not estimate	Not given
	% reduction	14%	Not calculable	Not given
Mean per patient discounted lenalidomide cost	No dose cap	£57,800	Not calculated	Not given
	2 year dose cap	£50,600	Not calculated	Not given
	% reduction	12%	Not calculated	Not given
Mean per patient undiscounted lenalidomide cost	No dose cap	£59,800	Not calculated	Not given
	2 year dose cap	£51,800	Not calculated	Not given
	% reduction	13%	Not calculated	Not given
% patients dose cap triggered		17%	17%	17%

§ Table 1 Celgene response to the ACD.

† Implemented by changing cell C28 in worksheet “Death 2prior the. Group” from 0.5 to 3.2.

Table 2: Comparison of results of Celgene models for >1 prior incl. thalidomide subgroup

		>1 prior therapy (incl. thalidomide)		
		Adjusted August model (ERG calcs)	December model (ERG calcs)	December model (Celgene calcs)
ICER (£/QALY) Dex OS fit to median MRC data	No dose cap	**32,200** (Incr. cost= £53,661, incr. QALY=1.66)	**31,000** (Incr. cost= £52,642, incr. QALY=1.70)	**30,900**§
	2 year dose cap	**30,600** (Incr. cost= £50,585, incr. QALY=1.66)	**29,100** (Incr. cost= £49,275, incr. QALY=1.70)	**28,900**§
ICER (£/LYG) Dex OS fit to median MRC data	No dose cap	21,400 (Incr. cost= £53,661, incr. LY=2.51)	20,500 (Incr. cost= £52,642, incr. LY=2.56)	20,500 (Incr. cost= £52,597, incr. LY=2.57)§
	2 year dose cap	20,300 (Incr. cost= £50,585, incr. LY=2.49)	19,300 (Incr. cost= £49,275, incr. LY=2.55)	Not given
ICER (£/QALY) Dex OS fit to mean MRC data†	No dose cap	**45,500** (Incr. cost= £52,331, incr. QALY=1.15)	**44,100** (Incr. cost= £51,049, incr. QALY=1.16)	Not given
	2 year dose cap	**42,400** (Incr. cost= £48,933, incr. QALY=1.15)	**41,300** (Incr. cost= £47,531, incr. QALY=1.15)	Not given
ICER (£/LYG) Dex OS fit to mean MRC data†	No dose cap	30,600 (Incr. cost= £52,331, incr. LY=1.71)	29,800 (Incr. cost= £51,049, incr. LY=1.71)	Not given
	2 year dose cap	28,600 (Incr. cost= £48,933, incr. LY=1.71)	27,800 (Incr. cost= £47,531, incr. LY=1.71)	Not given
Mean per patient	No dose cap	£48,400	£47,500	£47,500

discounted drug (Len+Dex) cost	2 year dose cap	£45,400	£44,100	£44,100
	% reduction	6%	7%	7%
Mean per patient undiscounted drug (Len+Dex) cost	No dose cap	£49,900	£48,800	Not given
	2 year dose cap	£46,400	Model does not estimate	Not given
	% reduction	7%	Not calculable	Not given
Mean per patient discounted lenalidomide cost	No dose cap	£48,500	Not calculated	Not given
	2 year dose cap	£45,200	Not calculated	Not given
	% reduction	7%	Not calculated	Not given
Mean per patient undiscounted lenalidomide cost	No dose cap	£49,800	Not calculated	Not given
	2 year dose cap	£46,300	Not calculated	Not given
	% reduction	7%	Not calculated	Not given
% patients dose cap triggered		11%	11%	11%

§ Table 1 Celgene response to the ACD.
† Implemented by changing cell C28 in worksheet “Death 2prior the. Group” from 0.5 to 3.2.

Comment on Celgene's defence of fitting the modelled overall survival for dexamethasone to the median, not the mean, of the MRC dexamethasone data

1) Celgene state that "Fitting has to do with what is most justifiable in terms of reproducing the information as accurately as possible, not with the use of the fits afterwards."

There are an infinite number of ways of fitting to the MRC OS dexamethasone data: e.g. to the mean, 25% percentile, 40th percentile, 50th percentile (median), 75% percentile, minimize sum squares of differences. We believe that it is important to choose the method which is most appropriate for use in the cost-effectiveness model. In this case, cost-effectiveness is driven by mean dexamethasone overall survival, therefore, we believe that the model should fit to the mean dexamethasone overall survival MRC data.

Indeed, we go further and say that it would have been preferable to design the model so that the model output gave a very close fit to the exponential curve for dexamethasone from the MRC data. However, this is not possible within the structure of the model because overall survival is constrained as the sum of two distributions: a Weibull distribution in PFS and an exponential distribution in PPS.

2) Celgene state: "It is not clear in the ERG report how they generated a different fit"

To fit to the mean dexamethasone OS MRC data, for >1 prior subgroup, we changed cell C28 in the worksheet "Death 2prior the. Group" from 0.5 to 3.2. This parameter adjusts post-progression survival from the MM RCTs to reflect the experience in the MRC data.

3) Celgene state: "Based on their Figure 6 (reproduced below) it appears that their calculations are incorrect as the curve representing our submitted model should cross the exponential curve from MRC exactly at the 50% survival point (i.e., the median) and it appears to cross at about 42% instead."

According to Celgene's stated aim of fitting to the median, the curve should indeed cross at the 50% percentile. However, although Celgene stated that they fitted to the median for the >1 prior therapy subgroup, in fact, the median dexamethasone overall survival is 13.3 months in their model - greater than the median of 11.6 months to which they were attempting to fit. Therefore, Celgene's model does not fit exactly to the median. This was Celgene's error, not ours.

For the 1 prior therapy subgroup, as Celgene stated, they fitted exactly to the median of 19.5 months.

4) Celgene state: "The exponential distribution from the MRC is not likely to be the true shape as it is well known that human mortality accelerates with time, requiring either a Weibull or Gompertz fit (Román et al. 2007; Jucket et al 1993). This was not a concern for our approach as we are not using the MRC-derived shape in the model. The only purpose of the MRC analyses was to provide a calibration point that would allow adjustment of the equations in the model to remove the cross-over effects. By calibrating to the mean produced by the MRC curves, the ERG is taking the exponential shape to be the true function of OS in multiple myeloma."

Celgene found that the exponential distribution fitted the MRC adjusted overall survival for dexamethasone very well for both the 1 prior and >1 prior patient subgroups. Indeed, in their original report, p53 of Appendix 8, Celgene state "the shape parameter of the Weibull distribution does not improve the fit of the models. In fact, the estimates of the shape parameters were 1.01 (95% CI: 0.96 – 1.07) and 0.98 (95% CI: 0.89 – 1.08) in the one prior and multiple prior groups, respectively.", and the exponential distribution has a shape parameter of 1. Therefore, although we acknowledge that human mortality sometimes requires a Weibull or Gompertz fit, as Celgene state, this is clearly not the case in this instance.

5) Celgene state: "Indeed, the ERG themselves, when adjusting the Len/dex survival calibrated to the median not the mean (pg 82)".

We did indeed adjust Len/dex overall survival to the median, not the mean. However, if the mean overall survival for the Len/dex treatment arm from the MM RCTs had been available, we would have calibrated the model to the mean, not the median. In this instance, the Len/dex overall survival was immature, with approximately 50% of patients still alive at data cutoff in the published data. Therefore, we were forced to use a different method to calibrate the modelled Len/dex overall survival. We used the next best option, and fitted to the median. Furthermore, Celgene's modelled Len/dex OS departs from the RCT OS not just at the median, but rather (as stated in our report and as can be seen in Figure 5 in our report), at all points from the 100th percentile to the 50th percentile.

6) Celgene state: "Given that the true OS distributions are right-skewed (most of the deaths happen early), calibrating to the mean ignores where most of the known deaths actually occur and overemphasizes the tail of the distribution where there are fewer

patients and much more uncertainty. Thus, the accuracy of predicted survival times in the known earlier parts of the curve would be compromised to gain better fit to the less well known, much more inaccurate, tail."

As mentioned above, cost-effectiveness is driven by mean (not median) overall survival. The mean, which is the area under the survival curve, can be heavily influenced by the tail of the distribution. Conversely, the median is completely independent of the tail. Therefore, it is important to take into account the shape of the tail of the Kaplan-Meier curve. By ignoring the tail, and concentrating solely on the median of the survival distribution, one effectively discards 50% of the available data.

The Kaplan-Meier curve for dexamethasone OS from the MRC data was constructed from the experience of 375 patients for the >1 prior therapy subgroup (p52 Appendix 8 Celgene submission). This is a substantial number of patients, and therefore we expect the tail of the curve to be reasonably accurate.

It is true that the tail of Kaplan-Meier curves may be more uncertain than the early part of the curve, but only when there is a large amount of censoring. However, we understand that there is virtually no censoring in the 375 patients: 354 (94.4%) of the 375 patients were recorded to have died (p52 Appendix 8 Celgene submission). Therefore, Celgene's assertion that the tail of the distribution is inherently inaccurate is unsustainable. In fact, there may be more uncertainty about the median than about the tail when there is very little censoring.

Furthermore, as stated above, the exponential curve fitted the data well, which implies that the exponential curve also fits the tail well.