in collaboration with:

# Lenalidomide for the treatment of myelodysplastic syndromes associated with deletion 5q cytogenetic abnormality

Addendum to Evidence Review Group's Report following Celgene's new evidence submission with approved patient access scheme of 8th November 2013


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# 1. Introduction

The Evidence Review Group (ERG) was requested by NICE to provide commentary and validity checks on the updated cost-effectiveness analysis submitted by the manufacturer, in light of the Department of Health approval for the patient access scheme (PAS). A number of detailed checks were undertaken to ensure the validity of the manufacturer's updated cost-effectiveness analysis.

# 2. New manufacturer evidence

**Details of the patient access scheme**

The approved PAS outlines that the manufacturer provides lenalidomide at no cost to the NHS for patients with transfusion dependent low- or intermediate-1 risk MDS with isolated del5q abnormality that remain on lenalidomide treatment beyond 26 cycles. The PAS reduces the long-term drug costs for patients that receive more than 26 cycles of lenalidomide. In the model, average drug costs are reduced to zero after 26 cycles of treatment.

**Summary of adjustments made to original manufacturer model**

The appraisal committee agreed to the various changes made by the ERG to the original model as submitted by the manufacturer resulting in a new ERG base case of £62,674. The committee accepted the suggestion of the ERG that monitoring visits occurred at a haematologist (£106) instead of a general practitioner (£36). This change resulted in an ICER of £64,079 without PAS (base case + monitoring).

During the appraisal process, a change was made to the ERG base case (+ monitoring), i.e. the rate of progression to acute myeloid leukaemia (AML) was decided to be kept equal in both transfusion independent and dependent patients and is based on the AML progression curve of transfusion independent patients. Thus, the initial benefit attributed to lenalidomide in lowering the rate of progression to AML is removed. This resulted in a new ICER of £67,102.

Using this ICER as a starting point, the manufacturer now has made two changes; one relating to the costs for monitoring visits and one regarding the PAS.

The ERG based costs for monitoring visits at a haematologist on the Payment by Results tariffs (based on clinical best practices) and used £106 in the ERG base case +monitoring. In the new submission from the manufacturer, the costs for monitoring visits of £159.56 were based on the NHS reference costs 2011/2012. The ERG agrees with the manufacturer that it is preferable to use average costs based on the NHS reference costs instead of the Payment by Results tariffs.

The PAS that has been implemented reduces the drug costs to zero for patients treated with lenalidomide beyond 26 cycles.

The following tables present the updated cost-effectiveness results including the revised monitoring visits at a haematologist (£159.56) without PAS and with PAS.

**Table 1 Cost-effectiveness results revised base-case without PAS**

| | Intervention | Best supportive care |
|---|---|---|
| Technology acquisition cost (drug costs) | £74,196 | £2,243 |
| Other costs | £98,111 | £120,999 |
| Total costs | £172,307 | £123,242 |
| Difference in total costs | N/A | £49,065 |
| LYG (Undiscounted) | 6.06 | 5.17 |
| LYG difference (undiscounted) | N/A | 0.88 |
| QALYs (Discounted) | 3.67 | 2.95 |
| QALY difference (Discounted) | N/A | 0.72 |
| ICER | N/A | £68,125 |
| LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio<br>QALYs and Costs are presented with a 3.5% discount rate. LYG are undiscounted. | | |

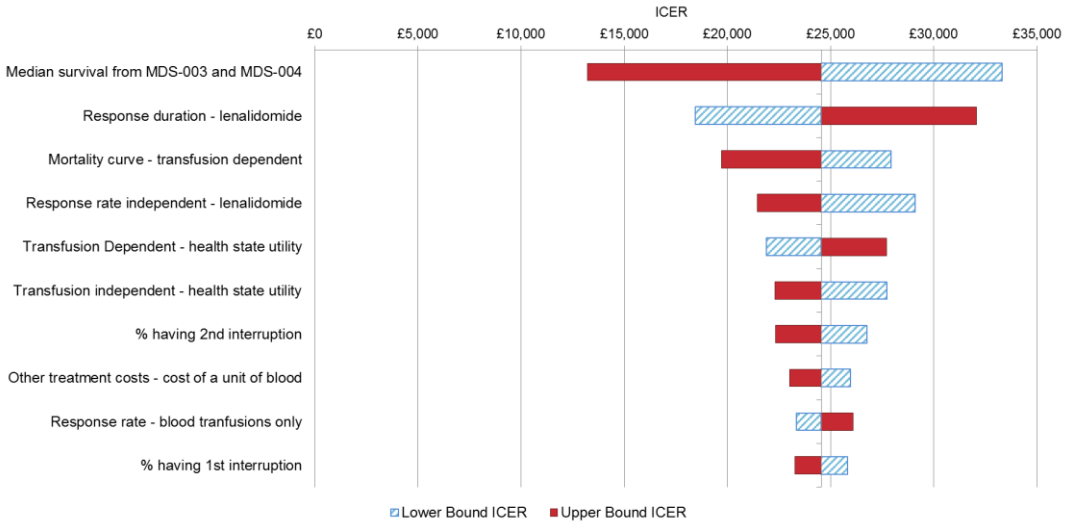
**Table 2 Cost-effectiveness results revised base-case with PAS**

| | Intervention | Best supportive care |
|---|---|---|
| Technology acquisition cost (drug costs) | £42,808 | £2,243 |
| Other costs | £98,111 | £120,999 |
| Total costs | £140,919 | £123,242 |
| Difference in total costs | N/A | £17,677 |
| LYG (Undiscounted) | 6.06 | 5.17 |
| LYG difference (undiscounted) | N/A | 0.88 |
| QALYs (Discounted) | 3.67 | 2.95 |
| QALY difference (Discounted) | N/A | 0.72 |
| ICER | N/A | £24,544 |
| LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio<br>QALYs and Costs are presented with a 3.5% discount rate. LYG are undiscounted. | | |

## Sensitivity analysis

Figure 1 shows the top 10 parameters affecting the ICER. The most influential parameter is the median survival from the MDS-003 and MDS-004 trials followed by the response duration of lenalidomide.

**Figure 1 Tornado diagram – top 10 parameters affecting the ICER with PAS**

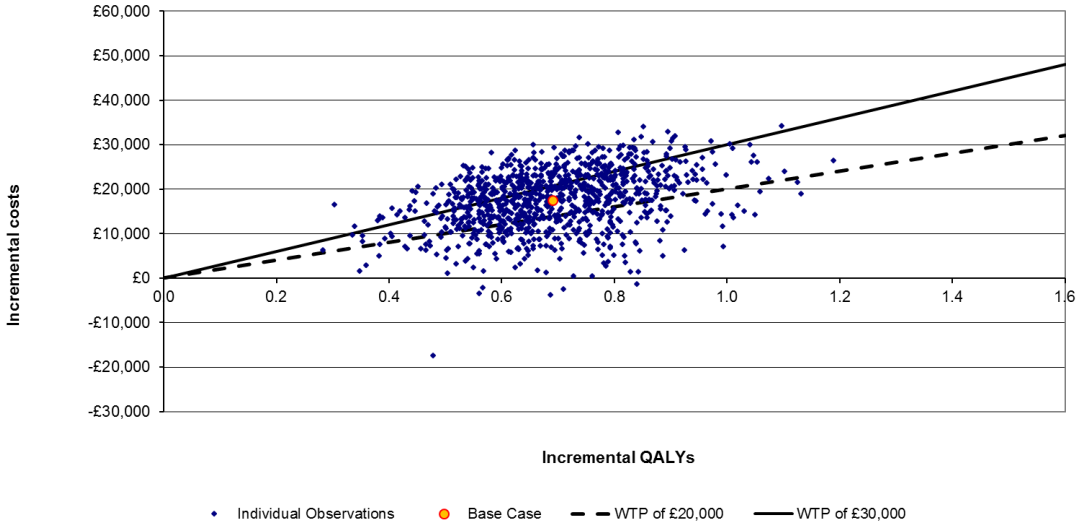



Probabilistic sensitivity analyses were conducted using 1,000 model runs. The mean ICER using probabilistic analysis was £25,468 per QALY, 65.8% of observations were cost-effective at a £30,000 per QALY threshold.

**Table 3 Output from PSA with PAS**

| | **With PAS** |
|---|---|
| Mean Incremental Costs | £17,573 |
| Mean Incremental QALYs | 0.690 |
| Mean ICER | £25,468 |
| % of observations cost-effective at £20,000 threshold | 24.6% |
| % of observations cost-effective at £30,000 threshold | 65.8% |

## Figure 1 Cost Effectiveness Scatter Plot with PAS




## Scenario analysis

The following tables present the scenario analysis.

## Table 4 All trial patients rather than UK patients with PAS

| Technology | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER |
|---|---|---|---|---|---|---|---|
| Best supportive care | £126,613 | 5.23 | 2.99 | - | - | - | - |
| Revlimid | £145,337 | 6.06 | 3.68 | £18,725 | 0.83 | 0.69 | £27,114 |

## Table 5 Comparator with PAS

| Curve | Technology | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER |
|---|---|---|---|---|---|---|---|---|
| All patients using ESA | Best Supportive Care | £131,509 | 5.34 | 3.04 | - | - | - | - |
| | Revlimid | £140,919 | 6.06 | 3.67 | £9,409 | 0.71 | 0.63 | £15,030 |
| All patients receiving only transfusions as required | Best Supportive Care | £120,521 | 5.11 | 2.92 | - | - | - | - |
| | Revlimid | £140,919 | 6.06 | 3.67 | £20,398 | 0.95 | 0.76 | £27,005 |

## Table 6 Iron chelation threshold with PAS

| Threshold | Technology | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER |
|---|---|---|---|---|---|---|---|---|
| 20 | Best Supportive Care | £121,964 | 5.17 | 2.95 | - | - | - | - |
| | Revlimid | £141,103 | 6.06 | 3.67 | £19,139 | 0.88 | 0.72 | £26,551 |
| 30 | Best Supportive Care | £123,767 | 5.17 | 2.95 | - | - | - | - |
| | Revlimid | £144,632 | 6.06 | 3.67 | £20,864 | 0.88 | 0.72 | £28,881 |

## Table 7 Source of Utilities with PAS

| Threshold | Technology | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER |
|---|---|---|---|---|---|---|---|---|
| Goss | Best Supportive Care | £123,241 | 5.17 | 2.31 | - | - | - | - |
| | Revlimid | £140,919 | 6.06 | 3.23 | £17,677 | 0.88 | 0.92 | £19,135 |
| Buckstein | Best Supportive Care | £123,241 | 5.17 | 2.99 | - | - | - | - |
| | Revlimid | £140,919 | 6.06 | 4.19 | £17,677 | 0.88 | 0.68 | £25,861 |

## Table 8 Curve selection – response duration with PAS

| Curve | Technology | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER |
|---|---|---|---|---|---|---|---|---|
| Exponential | Best Supportive Care | £123,235 | 5.17 | 2.95 | - | - | - | - |
| | Revlimid | £140,955 | 6.06 | 3.67 | £17,720 | 0.88 | 0.72 | £24,776 |
| Weibull | Best Supportive Care | £123,328 | 5.17 | 2.95 | - | - | - | - |
| | Revlimid | £142,954 | 6.06 | 3.65 | £19,626 | 0.88 | 0.70 | £27,899 |
| Log-logistic | Best Supportive Care | £123,265 | 5.17 | 2.95 | - | - | - | - |
| | Revlimid | £141,561 | 6.06 | 3.67 | £18,295 | 0.88 | 0.71 | £25,597 |
| Extreme Value | Best Supportive Care | £123,349 | 5.17 | 2.95 | - | - | - | - |
| | Revlimid | £144,120 | 6.06 | 3.64 | £20,771 | 0.88 | 0.69 | £30,022 |

## Table 9 Curve selection – AML Progression with PAS

| Curve | Technology | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER |
|---|---|---|---|---|---|---|---|---|
| Exponential | Best Supportive Care | £124,863 | 5.26 | 2.98 | - | - | - | - |
| | Revlimid | £143,647 | 6.24 | 3.74 | £18,785 | 0.98 | 0.76 | £24,808 |
| Log-logistic | Best Supportive Care | £125,283 | 5.28 | 2.99 | - | - | - | - |
| | Revlimid | £144,254 | 6.25 | 3.75 | £18,971 | 0.98 | 0.76 | £25,083 |
| Lognormal | Best Supportive Care | £127,893 | 5.40 | 3.05 | - | - | - | - |
| | Revlimid | £147,831 | 6.46 | 3.84 | £19,938 | 1.05 | 0.79 | £25,218 |
| Extreme Value | Best Supportive Care | £121,208 | 5.07 | 2.91 | - | - | - | - |
| | Revlimid | £137,618 | 5.86 | 3.59 | £16,410 | 0.79 | 0.68 | £23,979 |

## Table 10 Curve selection – overall survival with PAS

| Curve | Technology | Total costs (£) | Total LYG | Total QALYs | Incremental costs (£) | Incremental LYG | Incremental QALYs | ICER |
|---|---|---|---|---|---|---|---|---|
| Exponential | Best Supportive Care | £133,596 | 5.76 | 3.17 | - | - | - | - |
| | Revlimid | £148,842 | 6.60 | 3.87 | £15,247 | 0.84 | 0.70 | £21,881 |
| Log-logistic | Best Supportive Care | £127,292 | 5.39 | 3.04 | - | - | - | - |
| | Revlimid | £147,579 | 6.44 | 3.85 | £20,287 | 1.05 | 0.81 | £25,130 |
| Lognormal | Best Supportive Care | £130,724 | 5.57 | 3.12 | - | - | - | - |
| | Revlimid | £151,144 | 6.65 | 3.94 | £20,419 | 1.08 | 0.82 | £24,775 |
| Extreme Value | Best Supportive Care | £120,419 | 5.02 | 2.89 | - | - | - | - |
| | Revlimid | £135,647 | 5.75 | 3.53 | £15,229 | 0.73 | 0.64 | £23,614 |

## 3. ERG commentary

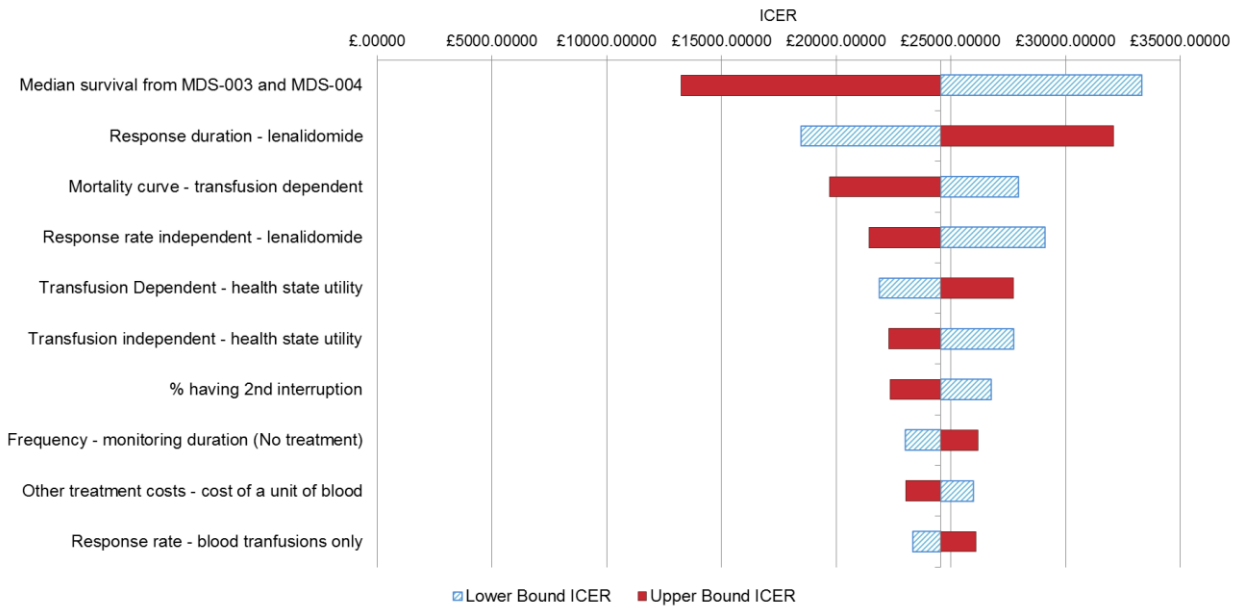
The ERG checked how the PAS worked and whether it was implemented properly. After 26 cycles of treatment with lenalidomide the drug costs become zero and according to the ERG the PAS was properly implemented in the economic model.

Minor adjustments to the sensitivity analysis were made by the ERG, as these were also made earlier in the ERG defined base case in the original assessment report, but were not included in the updated version of the manufacturers model:

- Uncertainty added to the frequency of monitoring visits
- Uncertainty increased around cost estimates complications and adverse events from 10% to 20%.

The results from the deterministic sensitivity analysis changed a little and now included the frequency of monitoring as one of the ten parameters that had the largest impact on the ICER.

**Figure 3 Tornado diagram – top 10 parameters affecting the ICER with PAS**




While the ERG was able to replicate the deterministic sensitivity analysis, the outcomes of the probabilistic sensitivity analysis were slightly different in the manufacturer's model and the ERG model, even after including the monitoring frequency and increasing the uncertainty around the cost estimates of complications and adverse events in the manufacturer's model.

We were able to deduct that this was caused by a (non-reported) change made in the manufacturer's model relating to the cycle in which transfusion dependent patients require chelation. We do however agree with the correction made by the manufacturer.

After including the monitoring frequency and increasing the uncertainty around the cost estimates of complications and adverse events in the manufacturer's PAS model, the average ICER of the PSA was £25,344. At a threshold of £20,000 per QALY, 26.2% of the simulations were cost-effective and at a threshold of £30,000, 66.6% of the simulations were cost-effective. This is comparable to the manufacturer's submitted PSA results of 65.8%.

In order to be complete, we also present the summary results of the additional scenario analysis conducted by the ERG in the original ERG report (the detailed results are in the appendix).

**Table 11 Additional scenarios explored by the ERG with PAS**

| Parameter | ERG Base case | Scenario analysis | ICER without PAS | ICER with PAS |
|---|---|---|---|---|
| ERG Base case | | | £68,125 | £24,544 |
| Utility value for transfusion dependence | Utility value fully transfusion dependent (0.65) | Utility value reduced transfusion burden (0.77) | £78,298 | £28,209 |
| Utility value for AML | Utility AML is similar to transfusion dependence (0.65) | Utility of AML is reduced with 25% (0.49) | £68,670 | £24,740 |
| Cost adverse events | Treatment cost adverse events | Zero cost for treating adverse events | £67,870 | £24,289 |
| Treatment of adverse events | Only a proportion of patients experiencing AEs require treatment | All patients experiencing AEs require treatment | £69,441 | £25,860 |
| Proportion of patients treated with IV chelation | 5.70% | 100% | £59,250 | £21,347 |
| Response duration BSC | According to 5mg | According to 10mg | £70,138 | £26,034 |
| Utility decrement AE | 0% Thrombocytopenia<br>0% Neutropenia | 25% Thrombocytopenia<br>25% Neutropenia | £69,622 | £25,084 |

## 4. Conclusions

The updated cost-effectiveness results show lenalidomide to be a cost-effective treatment for patients with low or intermediate-1 risk MDS at a threshold of £30,000.

Based on the cost-effectiveness results with PAS, using a threshold of £30,000, 65% of the observations in the probabilistic sensitivity analysis are cost-effective.

## Appendix 1: Additional ERG analyses

### Table A1 Detailed cost-effectiveness results of additional ERG scenarios with PAS

| | Best supportive care | | | Lenalidomide | | | Incremental | | ICER |
|---|---|---|---|---|---|---|---|---|---|
| | Cost | QALY | LYG | Cost | QALY | LYG | Cost | QALY | Cost per QALY gained |
| **ERG Base case** | **£123,242** | **2.95** | **5.17** | **£140,919** | **3.67** | **6.06** | **£17,677** | **0.72** | **£24,544** |
| Utility value for transfusion dependence | £123,242 | 3.47 | 5.17 | £140,919 | 4.10 | 6.06 | £17,677 | 0.63 | £28,209 |
| Utility value for AML | £123,242 | 2.92 | 5.17 | £140,919 | 3.63 | 6.06 | £17,677 | 0.71 | £24,740 |
| Cost adverse events | £123,242 | 2.95 | 5.17 | £140,735 | 3.67 | 6.06 | £17,493 | 0.72 | £24,289 |
| Treatment of adverse events | £123,242 | 2.95 | 5.17 | £141,866 | 3.67 | 6.06 | £18,625 | 0.72 | £25,860 |
| Proportion of patients treated with IV chelation | £123,242 | 2.61 | 5.17 | £140,919 | 3.44 | 6.06 | £17,677 | 0.83 | £21,347 |
| Response duration BSC | £122,391 | 2.96 | 5.17 | £140,919 | 3.67 | 6.06 | £18,528 | 0.71 | £26,034 |
| Utility decrement AE | £123,242 | 2.95 | 5.17 | £140,919 | 3.66 | 6.06 | £17,677 | 0.70 | £25,084 |