Royal College of Physicians

Tel:

From

c/o

31 July 2013

Dear

Re: Lenalidomide for the treatment of myelodysplastic syndromes associated with a deletion 5q cytogenic abnormality in people with red blood cell transfusion dependence [ID480] – Appraisal Consultation Document (ACD)

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 28,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

I write on behalf of the NCRI/RCP/RCR/ACP/JCCO/ who work together in responding to relevant NICE consultations. We are grateful for the opportunity to comment on the above ACD and would like to make the following comments.

Has all of the relevant evidence been taken into account?
The evidence base available to inform a precise ICER calculation is very limited and much of this is extrapolation. To our knowledge there is no more relevant evidence.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
Clinical effectiveness
The Appraisal Committee acknowledges the clinical effectiveness of lenalidomide for this indication specifically in promoting independence from red cell transfusion. The magnitude of haemoglobin response is not noted in the ACD but we believe was mentioned by the clinical expert in committee. This is worth noting given that the magnitude of haemoglobin increase, which is sustained by lenalidomide, is not normally achieved by alternative strategies to improve anaemia such as red cell transfusions or ESAs. Indeed red cell transfusion produces a cyclical symptomatic benefit but peak haemoglobin concentrations are rarely >110 g/l which are achieved for perhaps only one week in the typical four week cycle. In contrast most responders to lenalidomide achieve *sustained* haemoglobin concentrations >110 g/l for a median response duration of around 2 years.

The Committee clearly placed considerable emphasis on the comment by the clinical expert that although red cell transfusion dependence is an adverse risk factor for overall survival in MDS, it remains unclear if reversal of transfusion dependence can in turn overcome that decrement in overall survival. This statement

is correct but there are data that can be extrapolated from other treatments for anaemia in low-risk MDS, which indicate that responders to therapies that increase haemoglobin concentration may have improved survival compared with untreated patients. Such retrospective cohort comparisons have been published for ESA[1,2] and for antithymocyte globulin[3]. If this were correct, despite the methodological limitations of such comparisons, then it is plausible that lenalidomide could produce a similar benefit, particularly as the median duration of response to lenalidomide is similar to that of ATG and of ESAs. Naturally, it could be that these drugs select (responding) patients who will have a better overall survival without therapy but the same is true for any drug that is demonstrated to improve the overall survival of any ITT clinical trial test arm vs. control.

In section 4.14 the Committee consider that lenalidomide is not a 'step change' in the management of symptomatic anaemic patients with MDS and del(5q) because there is no clear evidence of an overall survival advantage. Our experts believe that Lenalidomide *is* a step change given the very high response rate and magnitude of haemoglobin increase in these patients. Because the dataset available to assess the clinical and cost effectiveness is very limited it is rather premature to deem this therapy to not be such a step change. We believe that this statement should be softened.

The Committee have chosen not to seek subgroups in which the benefit may be greater with lenalidomide. An example would be patients with platelets > 150 x 10^9/l who consistently have a higher response rate in all published series.

Cost effectiveness
Although not health economists we would like to make some comments regarding assumptions made by the company and by the ERG

- We are unclear why the company have used data from the 5mg lenalidomide arm to approximate response duration to BSC given that the response rate is still much higher than the BSC group itself and the duration of response appears to be similar to that of the 10mg lenalidomide arm (Figure 6 on p64 of Manufacturer's Submission)?
- In 3.27 ' It also noted that 1 dose reduction in the lenalidomide 10 mg group meant that patients received effectively the same dose as the 5 mg group.' This statement is incorrect; the median doses after 4 cycles were 5m in the 10mg arm and 2.5mg in the 5mg arm. Furthermore, one of the reasons for a higher response rate in the 10mg arm is likely to be dose intensity in the first cycle, which is clearly dose dependent and different between the two arms. It is therefore wrong to assume that doses were 'effectively' the same in both arms for patients who had one dose reduction in the 10mg arm. This does not affect the economic model significantly given that the cost of different tablet doses is similar. Dose interruptions (which would affect the differential costs between the both arms were it imbalanced) were more frequent in the 10mg arm than the 5mg arm.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
There is considerable uncertainty surrounding the modelling, primarily due to a lack of high quality utility and survival data. We do not consider the provisional recommendations to be 'sound' given these uncertainties but can understand that the ICER is not likely to be close to £30,000.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity
There is potential discrimination for MDS patients with del(5q) from the Jehovah's Witness community who will refuse blood product support for their anaemia and who could reasonably be expected to respond to lenalidomide.

References

1. *Park S, Grabar S, Kelaidi C, et al: Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. Blood 111:574-82, 2008*
2. *Jadersten M, Malcovati L, Dybedal I, et al: Erythropoietin and granulocyte-colony stimulating factor treatment associated with improved survival in myelodysplastic syndrome. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 26:3607-13, 2008*
3. *Sloand EM, Wu CO, Greenberg P, et al: Factors affecting response and survival in patients with myelodysplasia treated with immunosuppressive therapy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 26:2505-11, 2008*

Yours sincerely

[redacted]