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6th January 2014

Dear Members of Technology Appraisal Committee B,

Re: NICE Appraisal Consultation Document: Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis

Novartis would like to thank the National Institute for Health and Care Excellence (NICE) for the opportunity to respond to the draft appraisal consultation document (ACD) for alemtuzumab. We would also like to commend NICE for their overall rigorous approach to the consideration of the evidence and the request for extensive additional economic analyses in this case, which we feel are wholly justified given the evidence presented for this therapy.

We do have several points that we would like to raise with the Committee, however. The most important of these relate to the populations that are used in the comparison of alemtuzumab to fingolimod and the additional analysis requested on long-term retreatment rates. Please find our points detailed below:

1. Populations used in the Comparisons to Fingolimod

Inappropriate consideration of fingolimod

The manufacturer's submission for alemtuzumab is based around first line treatment of the active RRMS population, defined by this therapy's marketing authorisation. This does not represent the same population for which fingolimod is licensed and recommended by NICE: patients with highly active RRMS despite beta interferon treatment. The manufacturer's economic analysis for alemtuzumab versus fingolimod and natalizumab uses the whole RRMS population and compares the treatments as first line (Section 3.17), which is inappropriate given fingolimod's marketing authorisation and NICE recommendation as described above. Although it is reported that the manufacturer does acknowledge that fingolimod and natalizumab are restricted by their marketing authorisations to the specific high disease activity subgroups, we feel that it is still inappropriate and misleading to report the results of the whole RRMS first line comparison within the ACD and request that this is removed from the report.

Validity of the subgroup analysis of alemtuzumab

We are pleased to read that the Committee has critically appraised the quality and reliability of the subgroup analysis for alemtuzumab in patients with highly active disease. We would ask that further details of this subgroup analysis, such as the sample sizes, are made available within the ACD so that readers can appraise the reliability themselves and understand how the Committee came to their decision.

2. Long-term Retreatment Inputs

It was acknowledged in the ACD that the manufacturer's inputs for retreatment in the economic model may not reflect the situation in actual clinical practice. We are glad that NICE have requested that the manufacturer investigate this important issue further.

The ACD states that "The Committee heard from the clinical specialists that in the trials, the percentage of people who needed a third course [of alemtuzumab] was greater than the percentage who needed a fourth course, and that the trend of fewer people needing successive courses lasted up to 7 years (the median follow-up time for which data were available)." We have a few concerns over this statement:

a) Firstly, we are not aware of trial data for alemtuzumab that extends to 7 years, so would hope that the Committee is planning to look carefully into the source of this data, including the methodology of its collection, the potential biases that may occur, the sample size and the patient characteristics. We feel that it would be appropriate for a brief appraisal of this data source and its limitations to be included in the final report.

b) Secondly, we are unsure how the Committee is interpreting the need for a "time-dependent rate of re-treatment" in their request for this to be applied in the model. We agree that the rate of re-treatment is likely to be time-dependent: the risk of requiring a retreatment with alemtuzumab is expected to increase over time spent on treatment. This is supported by Alisdair Coles' statement that more patients would experience relapses and hence require re-treatment towards the end of the 7 year period than in years 3 or 4. We hope, therefore, that the Committee has requested an increasing rate of re-treatment over time, rather than a decreasing one. We note that this does not preclude a trend for fewer people needing successive courses, as is also supported by the evidence; it simply means that following each course, there will be a time-dependent increasing rate of re-treatment.

c) Thirdly, we would like to clarify our concern over whether the reference to 7 year data prevents re-treatments after 7 years from being included in the model. Whilst we acknowledge that retreatment rates in the long term are uncertain due to the lack of long-term data, some retreatment beyond 7 years would be expected and we feel that this should be investigated in the economic model. In cases of uncertainty, we were under the

impression that conservative assumptions should be applied, which in this case would be a high retreatment rate in the long term (ie. beyond 7 years).

3. Monitoring

We have several points for consideration with regards to monitoring costs and adherence to monitoring:

a) We are surprised that the monitoring costs for alemtuzumab used in the model are reported as lower than those for fingolimod and natalizumab for year 1, and lower than all DMTs, including beta-interferon and glatiramer acetate, in years 2+. This does not appear consistent with the extent of discussion on monitoring requirements for alemtuzumab at the NICE Committee meeting where all the clinical experts agreed that monitoring is a considerable issue. For example, the risk of experiencing a serious thyroid adverse event with this therapy was noted as increasing from years 2 – 4, which appears to contradict lower monitoring costs in year 2.

   The summary of product characteristics for alemtuzumab specifies several laboratory tests that should be performed for patients who have received this treatment.[1] These have been costed by the manufacturer (as outlined in the manufacturer's submission), but given the views of the clinical experts, it seems likely that there are additional montoring costs that have not been accounted for by the manufacturer.

b) We are disappointed that the ERG has presented its monitoring requirements of 4 visits in the **first year** and 2 annually thereafter as "a worst case scenario". Alasdair Coles noted that monitoring would in fact be higher than this (4 visits in the first **2 years**, then 2 visits annually with monitoring reset upon retreatment). If this is the monitoring that is required to offset the risks associated with use of alemtuzumab then this input should represent the basecase of the appraisal and not be presented as the "worst case".

c) If adherence to monitoring is not maintained, which is highly likely according to both clinical experts and patient experts, then side-effects may well be above those seen in clinical trials and incorporated in the manufacturer's model. A further consideration is that monthly monitoring may well not identify all serious side-effects of the drugs, for example because platelet counts can drop very suddenly in the period between monitoring visits. We are unclear whether the model captures these risks.

d) Given the uncertainty over both the long-term safety implications of alemtuzumab and the extent of adherence to monitoring that will occur in clinical practice, we propose that, should a positive recommendation for alemtuzumab ultimately be provided, NICE consider recommending that a dedicated registry is set up to ensure that all safety signals in patients treated with this therapy are captured and analysed (as has been done in previous cases, such as in TA103[2]). This would

be the only way for the NHS to be confident that they are adequately monitoring a therapy that could have very serious long term side effects that are currently unknown. Furthermore, given that there is 7 years of clinical experience for alemtuzumab available from UK patients, it would also seem advisable to perform a retrospective review of this data from a pharmacovigilance perspective. The need to understand more fully the safety profile of alemtuzumab has been highlighted in the recent Food and Drug Administration (FDA) assessment report of this intervention in the USA.[3]

4. Additional Points for Consideration

We are pleased to see that the Committee is considering issues regarding renal complications and post-alemtuzumab treatment with bone marrow transplant (BMT). We have provided some additional points for consideration below on each of these topics, which may aid future discussions. We also note below a clarification over definitions of high disease activity subgroups.

Renal complications

We agree with the Committee that given the clinical experts' concerns over renal complications, these should be included within the economic model. We have noticed, however, that the request for analysis focusses only on including the additional **costs** of renal complications. We hope that the **utility** implications of such serious adverse events are also being considered.

Bone Marrow Transplant

It was noted that bone marrow transplant (BMT) is the treatment option most likely to be employed following a lack of success with alemtuzumab. We would like to highlight that this is an expensive treatment option and one associated with considerable morbidity and mortality.[4] We are concerned over the impact of introducing alemtuzumab as a routine treatment, where there is a possibility that the routine following treatment would be such a drastic intervention as BMT. We also hope that the full costs of BMT (approximately £30,000 per procedure in the UK[5]) and disutility will be incorporated into the model.

Definitions of high disease activity subgroups

It has come to our attention that the ACD does not fully define the high disease activity subpopulations for which fingolimod and natalizumab are indicated and recommended. As not all readers of the ACD will be familiar with the difference between highly active disease despite beta-interferon and rapidly evolving severe RRMS, we would suggest it might be beneficial to clarify the full definitions by providing in the ACD the definitions presented in TA127[6] and TA254[7], or by referring to these previous technology appraisals in which the full definitions can be found.

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Summary

Novartis are reassured to see that the Committee has critically appraised the evidence for alemtuzumab and requested many important additional economic analyses. To summarise the main points that we would like to raise to the Committee following review of the ACD:

- There are cases within the ACD where fingolimod has been considered in a population outside of its marketing authorisation, namely in a first-line population and in the whole RRMS population.
- In terms of long-term re-treatment, we hope the Committee will appraise the source of evidence for 7 year exposure as cited by the clinical expert and consider the increased risk of re-treatment over time.
- We were surprised that for the monitoring costs used by the manufacturer, the cost for alemtuzumab used in the model was reported as lower than that for fingolimod and natalizumab for year 1, and lower than all DMTs, including beta-interferon and glatiramer acetate, in years 2+, which does not seem consistent with the discussions held at the appraisal meeting. Additionally, the ERG has included a lower estimate for neurology visits for alemtuzumab patients in their worst case than is expected in clinical practice as stated by one of the clinical experts.

Yours sincerely

[redacted]

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[1] Alemtuzumab summary of product characteristics
[2] NICE. Etanercept and efalizumab for the treatment of adults with psoriasis (TA103). Guidance issued July 2006 (available at: http://publications.nice.org.uk/etanercept-and-efalizumab-for-the-treatment-of-adults-with-psoriasis-ta103/guidance)
[3] Food and Drug Administration: Center for Drug Evaluation and Research. Peripheral and Central Nervous System Drugs Advisory Committee Meeting: Alemtuzumab (BLA 103948\5139) Background Package. Novermber 13, 2013.
[4] Daikeler T. et al. Complications of autologous hematopoietic stem cell transplantation for patients with autoimmune diseases, *Pediatric Research*. 2012;71(4 Pt 2):439-44
[5] Tappenden P. et al. Autologous haematopoietic stem cell transplantation for secondary progressive multiple sclerosis: an exploratory cost-effectiveness analysis. *Bone Marrow Transplant.* 2010;45(6):1014-21
[6] NICE. Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis (TA127). Guidance issued August 2007 (available at: http://publications.nice.org.uk/natalizumab-for-the-treatment-of-adults-with-highly-active-relapsingremitting-multiple-sclerosis-ta127)
[7] NICE. Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis (TA254). Guidance issued April 2012 (available at: http://publications.nice.org.uk/fingolimod-for-the-treatment-of-highly-active-relapsingremitting-multiple-sclerosis-ta254)