NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Dimethyl fumarate for treating relapsing-remitting multiple sclerosis [ID585]

Dear David,

The Evidence Review Group, the Centre for Reviews & Dissemination and Centre for Health Economics at the University of York, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 28th May 2013 by Biogen Idec. In general terms they felt that it is well presented and clear. NICE and the ERG note that the submission by far exceeds the recommended length of STA submissions. The ERG has exceptionally agreed to critique your submission as it is, in order to avoid any delays in the schedule of this appraisal. However, we have to emphasise at this stage to you that because of the length of your submission we cannot guarantee that Committee members are able to review your entire submission, and that the ERG is able to go through all aspects of your submission to the same degree of detail.

Despite the length of the submission, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **5pm** on **28th June 2013**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

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

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Martyn Burke, Technical Lead (martyn.burke@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (jeremy.powell@nice.org.uk) in the first instance.

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Yours sincerely

Elisabeth George
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Section A: Clarification on effectiveness data

Search strategy

A1. On page 37 of the manufacturer's submission (MS) and Appendix 2 (page 291 of the MS) it lists the databases searched, please state the service providers used for each database.

A2. Section 10.2.5 (page 294 of the MS) summarises the additional searches carried out by the manufacturer for the evidence presented in Section 6.1 of the MS. Please provide details of search terms (if any) used for searching Clinicaltrials.gov, metaRegister of Controlled Trials, and the NICE website.

A3. Page 37 of the MS suggests that a number of conference proceedings were searched for the evidence presented in Section 6.1 of the MS. Please clarify how each of the named conferences were searched. Please confirm whether they were searched using a website – (if so, what search terms were used), or hand searched as paper copies (if so, what volumes were used).

A4. Section 6.8 (and Appendix 6, page 302 of the MS) provides details of the additional searches carried out for non-RCT evidence. Please state how each of the named conferences were searched. Please confirm whether they were searched using a website – (if so, what search terms were used), or hand searched as paper copies (if so, what volumes were used).

Mixed treatment comparisons

A5. **Priority Question:** Please provide a list of studies excluded from the review of RCTs for the mixed treatment comparison (MTC) together with reasons for exclusion.

A6. **Priority Question:** The description for the SAS code for the MTCs with binomial outcomes, page 343 of the MS, states that adjustment may have been made for the G matrix. Please clarify if this was done for every analysis with a binomial outcome. If not, please clarify for which analyses it was done.

A7. **Priority Question:** The outcomes of the MTC and the effectiveness data use in the economic model are not clear. Specifically:

a) The use of the logit function in the SAS code for the MTCs with binomial outcomes, pages 342 to 343 of the MS, suggests that the results of the analyses would be odds ratios. The results of the MTCs, pages 139 to 152 of the MS, indicate that a risk ratio was the outcome for binomial outcomes. Please state:

i. what the outcomes of the binomial analyses were (odds ratios/risk ratios); and,

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ii. if relative risk outcomes were derived, please explain how they were derived.

b) The effectiveness outcome for disability progression used in the economic model is not clear. Firstly, the transition probabilities are converted to rates and adjusted by applying a disability progression rate relative to placebo. This rate ratio appears to be the same as the risk ratio in Table 50, page 180 of the MS. Secondly, in Section 7.6.3, page 216 of the MS, it states that hazard ratios were used for disability progression. Please explain:

i. whether you intended to use rate ratios or risk ratios in the model;
ii. if you intended to use risk ratios, what the rationale was (as opposed to using a hazard ratio);
iii. if you intended to use rate ratios, how these were derived; and
iv. if the model has been incorrectly specified, please correct it and report the corrected results.

A8. **Priority Question:** There appears to be some inconsistency between results reported in the submission.

a) Please clarify whether the MTC results reported in pages 139 to 152 of the MS were adjusted for covariates or unadjusted and whether these are the results that are used in the economic model.

b) If the results on pages 139 to 152 of the MS are the unadjusted results, there appear to be inconsistencies between these results and those reported in Tables 112 to 122, on pages 350 to 356 of the MS. Please clarify the apparent discrepancies between the results.

c) Please present the results of the MTC analyses for all comparators versus placebo as well as versus dimethyl fumarate.

d) In Table 52 (page 183 of the MS) some of the relative risks for intervention versus placebo and annual discontinuation risk values appear inconsistent with each other.

i. Please check all the values in Table 52, page183 of the MS, for consistency and provide correct data if there are errors, and
ii. Ensure that these are derived from the correct MTC results.

A9. **Priority Question:** Please indicate how the covariates included in the MTC covariate analyses (pages 344 to 349 of the MS) were specified as this is unclear for some of the variables. Please clarify whether the covariates were continuous or discrete, and if a variable was discrete please provide details of how it was defined.

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A10. Figure 57, page 360 of the MS, is labelled as "analyses of confirmed disability progression sustained for 3 months at 24 months". It appears that this may be the network for 6 months sustained disability. Please clarify whether this is correct.

A11. Please provide the rationale for including teriflunomide in the MTC to strengthen the placebo arm but not including other interventions such as alemtuzumab and laquinimod.

Non-RCT evidence

A12. Page 40 of the MS states that two records of non-RCTs were identified and the reader is referred to Section 6.2.7. These are described in Section 6.2.7. and a quality assessment of each is provided in Appendix 7 (page 306 of the MS). . However, Section 6.2.7 (page 47 of the MS) states that no non-RCTs were considered relevant and there is no discussion of the results of these two studies in the body of the submission.

- Please clarify whether any non-RCT evidence was included in the review of dimethyl fumarate, either providing appropriate details of the two included studies or a justification for excluding those identified.
- Only one of the two non-RCTs in Appendix 7 is included in the reference pack (Schimrigk, 2006). Please provide a copy of the other non-RCT (Macmanus, 2011).

Other

A13. The draft European Public Assessment Report (EPAR) includes some limited interim data from study 109MS303 up to August 2011. Please provide the results of any more recent analyses available from this study for annualised relapse rate (ARR), Expanded Disability Status Score (EDSS) progression sustained at three months, and occurrence of adverse events.

<u>Section B: Clarification on cost-effectiveness data</u>

Search strategy

B1. Section 7 (and Appendix 10, page 316 of the MS) suggests that a number of conference proceedings were searched to identify cost effectiveness studies. Please state the date ranges for conference searching. Please confirm how each conference was searched? Please clarify whether they were searched using a website – (if so, what search terms were used), or hand searched as paper copies (if so, what volumes were used).

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B2. Section 7.4.5 (and Appendix 12, page 336 of the MS) suggests that a number of conference proceedings were searched to obtain measurement and valuation of health effects data. Please state the date ranges for conference searching. Please confirm how each conference was searched? Please clarify whether they were searched using a website – (if so, what search terms were used), or hand searched as paper copies (if so, what volumes were used).

Economic model assumptions

B3. Please clarify if the risk at 2 years of '3 months sustained disability progression', 'adverse events' and 'discontinuation', have been assumed to apply at 1 year in the model.

B4. Please justify the selection of Pokorski et al 1997 to provide the mortality multipliers stated on page 179 of the MS.

Healthcare resource use

B5. **Priority Question:** Please provide the model code and the model output for the seemingly unrelated regressions (SUR) used to derive the EDSS and relapse state costs.

B6. **Priority Question:** Sections 7.5.3, (page 203 of the MS) and 7.5.6, (pages 206 to 211 of the MS): state that resource use was estimated using the UK MS Survey:

- Please clarify whether the reference (reference number 128) provided for the MS survey in section 9 of the MS is correct, as the reference refers to utility. If this is the incorrect reference, please highlight the publication that contains the 115 different resources included in the costs in the economic model.
- Please provide the number of patients used in the UK MS Survey to derive the resource estimates, including the proportion of patients in tertiary care, and the period over which data were collected for those patients.

B7. **Priority Question:** Please state how the costs were adjusted to be consistent with a 12 month cycle (Section 7.5.6, page 206 of the MS).

Results

B8. **Priority Question:** Please present mean incremental cost-effectiveness ratios (ICERs) from the probabilistic sensitivity analysis (PSA) using 10,000 iterations and explain any significant differences between the PSA and the deterministic results.

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Probabilistic sensitivity analysis

B9. **Priority Question:** Distributions need to be specified for the PSA. Section 7.6.3, (page 216 of the MS) states that relative risks and relapse rates were varied using the confidence intervals (CIs). Please confirm what distributional assumptions were made? Were they uniform? If so, please explain that choice.

B10. Please explain the rationale for assuming a 10% standard error (SE) for the beta distribution for the utility data rather than using the variance data available from the DEFINE and CONFIRM trials.

B11. Please provide the rationale for assuming a 10% SE for the natural history relapse rates and for the risk of discontinuation rather than of using the variance data available from the MTC.

Section C: Implementation

C1. Please provide the rationale for the assumption (Section 8.2, page 276 of the MS) that 100% of the population eligible to receive treatment would receive interferon or glatiramer acetate treatment, given that fingolimod and/or natalizumab are treatment options for people whose disease meets the criteria specified in NICE technology appraisals 127 and 245 , and that a minority of people may refuse treatment with disease modifying therapy (DMT) or it may be considered an inappropriate treatment.