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Dear [redacted]

Re: Single Technology Appraisal – Fingolimod for the treatment of relapsing-remitting multiple sclerosis

The Evidence Review Group (Centre for Reviews and Dissemination (CRD)) and the technical team at NICE have now had an opportunity to take a look at the submission by Novartis received on 18 March 2011. In general terms they felt that it is well presented and clear. However, 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 Tuesday 19 April 2011**. 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 Gabriel Rogers – Technical Lead (gabriel.rogers@nice.org.uk). Any

procedural questions should be addressed to Jeremy Powell – Project Manager (jeremy.powell@nice.org.uk) in the first instance.

Yours sincerely

Elisabeth George
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Population

Three populations (1a, 1b and 2; first introduced on p. 27) are suggested for consideration in your submission:

1) *Adult patients with relapsing-remitting multiple sclerosis (RRMS), with high disease activity despite treatment with a beta-interferon. These patients may be defined as those whose disease did not respond to a full and adequate course (normally at least 1 year of treatment) of beta-interferon.*

    a. *Patients with at least 1 relapse in the previous year while on therapy and have had at least 9 T2-hyperintense lesions in cranial MRI or at least 1 gadolinium-enhancing lesion.*

    b. *Patients with an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year.*

2) *Adult patients with rapidly evolving, severe, RRMS defined by 2 or more disabling relapses in 1 year and with 1 or more gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous recent MRI.*

A1. **Priority request:** For the individual arms of the FREEDOMS and the TRANSFORMS trials separately:

a. please state the numbers of patients and provide baseline characteristics[a] and outcome data[b] for each of the following populations:

- Population 1a
- Population 2
- Population 1a and 1b combined

b. please also state the numbers of patients and provide baseline characteristics[a] and outcome data[b] for each of the following populations:

- Population 1a but not 2 (i.e. excluding patients with RES)
- Population 1b but not 2 (i.e. excluding patients with RES)

A2. **Priority request:** Please provide an updated version of the graph in figure 10, along with the underlying data table, showing

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[a] *Baseline characteristics* should be understood to include: age, sex, disease history (including duration of MS and prior relapse history), prior exposure to DMTs and full details of initial EDSS distribution (i.e. number of participants at each EDSS level)

[b] *Outcome data* should be understood to include: numbers of participants experiencing both **primary and secondary outcomes** in each trial arm, together with Annualised Relapse Rates (ARRs), Annualised Progression Rates (APRs) and **relative effect measures** (e.g. hazard ratios) with SEs or confidence intervals for inter-arm comparisons in each case. Please also include **MRI data**, **quality of life data** and **details of discontinuations** for each group.

a. the distribution of patients across EDSS states separately for populations 1a, 1b and 2 from the pooled analysis of the FREEDOMS and TRANSFORMS trials, alongside the relevant populations from the London Ontario cohort, the UK MS Survey and the UK RSS prospective cohort study (with all relevant adjustments applied to each of these to give the populations as used in the model).

b. Please also provide the same data for populations 1a and 1b **excluding** any RES patients.

A3. **Priority request:** For each of the populations identified in A1.a and A1.b, above, please supply time-to-event data (e.g. Kaplan–Meier plots analogous to those provided in Figures 4 and 5 of your submission) for time to first relapse and time to progression. Please specify numbers at risk at each timepoint.

A4. **Priority request:** Please report a fully incremental analysis of the cost-effectiveness results for fingolimod in population 1b compared with all relevant comparators including optimised standard care with no disease modifying therapy.

A5. **Priority request:** Please also report a fully incremental analysis of the cost-effectiveness results for fingolimod compared with all relevant comparators including optimised standard care with no disease modifying therapy for the following populations:

a. Population 1a

b. Population 2

c. Population 1a but not 2 (i.e. excluding patients with RES)

d. Population 1b but not 2 (i.e. excluding patients with RES)

A6. **Priority request:** Please provide EDSS transition matrices (similar to tables 49 and 51 in the submission) and time to first progression (similar to figure 5B in the submission) derived using the data matching population 1b for each arm of the FREEDOMS trial.

Section B: Comparators

B1. **Priority request:** The results from the electronic model report an Incremental Cost-Effectiveness Ratio (ICER) of £279,107 per Quality Adjusted Life Year (QALY) for Avonex (interferon beta-1a) compared with best supportive care (optimised standard care with no disease modifying therapy) in the main modelled population. Please discuss the potential reasons why this estimated ICER appears significantly higher than the ICER estimates for beta interferons reported in previous NICE technology appraisals (NICE, 2002).

B2. Please clarify the reasons for choosing Avonex (interferon beta-1a) as the main comparator drug for fingolimod; please make reference to Avonex's relatively small market share of RRMS treatments, as provided in table A7 and the potential generalisability of this comparison to other disease modifying treatments that are used in the NHS.

B3. Glatiramer acetate is discussed in the submission as a treatment to be used in populations where patients do not respond to beta-interferons (e.g. p. 196). It has also been used as the comparator in similar non-responder populations in previous NICE technology appraisals (NICE, 2007). Please clarify why glatiramer acetate has not been formally included as a comparator in the economic model.

Section C: Health Related Quality of Life

C1. **Priority request:** The submission states that EQ5D data were collected from patients in both the FREEDOMS and the TRANSFORMS trials. Please add to table 59 additional columns representing the utility estimates from the EQ5D data from the FREEDOMS and TRANSFORMS trials.

C2. **Priority request:** Please provide the EQ5D data for patients in the populations identified in A1.a and A1.b, above.

Section D: Economic Model

Adverse Events

D1. Please provide more details on the specific events referred to in table 62 on utility decrements for adverse events. What events are included and what assumptions are made about their incidence in the modelled population?

Costs

D2. Please clarify how the administration cost of natalizumab (quoted in table 68 as £16,861) has been estimated. Please report the resource use assumptions, unit costs and data sources which have been used to derive this estimate.

Model structure

D3. The ERG's clinical advisor has emphasised that in RRMS, disability accumulates after relapses. Please clarify how this correlation between progression and relapses is accounted for in the decision model, taking into consideration the fact that different data sources (Ontario (Weinshenker,1989) for progression and Patzold and Pocklington (1982) for relapse) were used for the different outcomes.

D4. Please explain the statement in section 6.2.3 of the submission that states: "progression and relapses are applied separately in the model so that progression has no influence on relapse events" with reference to tables 49 and 55 from the same sub-section of the submission showing that both relapse rates and progression depend on EDSS states. Additionally, please comment on the implications of using a relative measure of effectiveness for both relapse and progression.

Section E: Minor queries and typographical errors

E1. Please provide clarification of the numbers of records identified in the systematic review: there are discrepancies between figure 1 and the text and figure 1 lacks internal coherence.

E2. P45: [redacted] of subjects... qualify for either definition of high disease activity". Please clarify which figure refers to FREEDOMS and which to TRANSFORMS.

E3. For tables 26 and 28 please provide confidence intervals for the ARR in subgroups.

E4. Please clarify the source of the % figures in table 47.

E5. The total number of patients in table 14 (Randomised population of FREEDOMS) = 1272 but table 18 (subgroup of patients with disease modifying treatment in previous year and unchanged/increased relapse rate or ongoing serious relapses) = 1292. The ERG assumes this is a typographical error; please provide the correct numbers.

References

National Institute for Clinical Excellence (NICE). Beta interferon and glatiramer acetate for the treatment of multiple sclerosis. Technology Appraisal Guidance No. 32. January 2002. Available at: http://www.nice.org.uk/nicemedia/live/11441/32290/32290.pdf

National Institute for Clinical Excellence (NICE). Multiple sclerosis - natalizumab: Evaluation report - Evidence Review Group Report. March 2007. Available at: http://www.nice.org.uk/nicemedia/live/11701/35004/35004.pdf

Patzold U, Pocklington PR. Course of multiple sclerosis. First results of a prospective study carried out of 102 MS patients from 1976-1980. Acta Neurol Scand 1982;65(4):248-66.

Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study, I: clinical course and disability. Brain 1989;112(pt 1):133-46.