CRD and CHE Technology Assessment Group

Fingolimod for the treatment of relapsing remitting multiple sclerosis

16th September 2011

Response to Manufacturer's Comments on ACD

The manufacturer has submitted a response dated 26th August 2011 to the draft document titled: Fingolimod for the treatment of relapsing remitting multiple sclerosis (RRMS) – Appraisal Consultation Document (ACD) produced by NICE. The ERG was requested by the Institute to provide additional commentary and validity checks on the comments on the ACD provided by the manufacturer. It should be recognised that the work undertaken by the ERG does not constitute a full critique of the manufacturer's commentary and does not accord with the procedures and templates applied to the original submission due to the limited time available to review the comments.

The manufacturer's response is divided into four sections A-D. Sections A, B and C represent differences in opinion between the ERG's assessment of the manufacturer's modelling assumptions as presented in the ERG report and the manufacturer's own views on these assumptions. The ERG does not feel that any new evidence has been presented that alters the ERGs original assessment of these assumptions.

Section A deals with the appropriateness of Avonex as a comparator. The manufacturer has selected and presented the results of head to head studies of varying designs which show no statistically significant difference between Avonex and other interferons (no details of the study populations are provided). These do not appear to have been systematically identified, nor have they been quality assessed. The ERG's primary point about the differing populations of the trials represented remains unchanged. The systematic reviews discussed were not mentioned in the original submission; the ERG discussed 2 of them in addition to another review to which the manufacturer does not refer (section 3.3, ERG report). The unique benefits in antibody production, liver enzyme elevations and injection site reactions refer to data which although available were not presented in the manufacturer's original submission; the ERG has not assessed this data and so is unable to comment. The ERG report noted both the prescribing data in the manufacturer's original submission and that provided in their responses to queries and clarifications and noted the populations to which it referred.

Section B deals with the appropriateness of best supportive care (BSC) as a comparator. As stated in the ERG report, the final scope issued by NICE stated that the comparators should be considered to be "interferon-beta, glatiramer acetate and optimised standard care with no disease modifying treatment. In addition, for people with rapidly evolving severe RRMS, natalizumab". The ERG report, and hence the ACD, reflect the fact that the submission is incomplete as it considered only one form of

interferon-beta (Avonex). The ERG's clinical advisor has indicated that comparators should include glatiramer acetate and other forms of interferon-beta in addition to Avonex. This reflects the views expressed by the clinical expert at the appraisal committee that switching between DMTs following unsatisfactory response is part of current clinical practice. Clearly for patients meeting the criteria for population 2 (RES patients) the appropriate comparator remains natalizumab. Despite the possibility of treatment switching to alternative DMT, for some patients BSC will remain a valid option following failure to respond adequately to a given interferon; an indication of this is provided by the significant proportion of RRMS patients in receipt of BSC. Therefore its inclusion in the scope and the ERG's revised model remain appropriate.

Section C deals with the appropriate population for the appraisal of fingolimod. The ERG notes the manufacturer's contention that population 1b but not 2 is inappropriate. Natalizumab is recommended by NICE for the whole of population 2, thus including patients in population 2 and 1b. Therefore the ERG's view that 1b not 2 is the appropriate population to be assessed using an interferon comparator stands. The ERG has already acknowledged the typographical error that described inferiority to placebo in population 1b rather than in 1b but not 2.

Section D of the manufacturer's response is an attempt to address the ERG's concerns around the transparency of the data selection process, the lack of justification around the methods utilised and the general lack of robustness of the model to changes in assumptions. This section contains four quantitative responses to the ERGs observations on the manufacturer's original submission. Understanding these four points and the implications of these will be the focus of what follows. The full list of the 36 key critiques and uncertainties that the ERG identified when appraising the manufacturer's cost-effectiveness analysis is presented in table 33, section 5.2.13 of the ERG report.

The first two quantitative responses are from section D3 and D6 of the manufacturer's comments. The ERG was concerned that the manufacturer had not justified the selection of data sources for the input parameters of the model and in many cases there were several possible parameter values to choose from, the choices made were often different to those made in other similar studies, and the choices made could have impacts on cost-effectiveness estimates. Sections D3 and D6 highlight two such instances among many where the manufacture has tried alternative parameter values in the model and recalculated cost-effectiveness estimates.

In section D3 the manufacturer sets the cost of relapse to £0 and notes that the ICER against Avonex (presumably deterministic results in population 1b) increases from £55,634 to £59,938. In section D6 the manufacturer increased the number of neurology visits for fingolimod patients to 6 (it is unclear from the document why 6 was chosen) and this was shown to increase the ICER against Avonex from £55,634 to £56,534.

The partial exploration of these uncertainties have in both cases been shown to change (increase) the cost-effectiveness estimates. In response to this evidence the ERG would like to highlight that these results agree with other explorations conducted by the ERG showing that cost effectiveness results are sensitive to alternative assumptions made. We would like to highlight that these are two selected uncertainties among many identified in the ERG report in the context of input data uncertainties.

Section D7 addresses the utility data used in the model. The ERG had concerns that the model was very sensitive to the utility data used and that the manufacturer had overlooked the utility data collected in their trials in favour of those produced for a different population in a different study. The ERG has explored this issue and shown a variety of model predictions based on alternative methods of incorporating the trial based utility values into the model in section 6.7 of the ERG report. In this comment, the manufacturer has selected the one method from among those presented by the ERG that is most favourable to the ICER estimates of fingolimod and applied this to show that the ICER against Avonex can improve from £55,634 to £52,982/£52,866 when using trial data in a specific way.

In response to this evidence the ERG would like to re-state that the model is very sensitive to changes in utility input data: a number of alternative, plausible scenarios for incorporating trial utility data into the model were explored in the ERG report returning significantly different results. The key point is that since the model predictions are highly sensitive to the estimates used it is crucial to fully justify both the data sources and any imputation methods used to generate these predictions.

Section D9 is a response to the ERG's concern with the use of relative risks in place of hazard ratios in the manufacturer's model. Refer to section 5.2.10 of the ERG report for a full discussion of this issue. The manufacturer has not addressed the ERG concerns in their response. They explain in the response that they have applied the hazard ratio value as a relative risk to the deterministic model. There are a number or problems with this analysis; firstly hazard ratios need to be applied as hazard ratios rather than as relative risks – full details of how to do this in the context of the manufacturer's model are detailed in section 6.1 of the ERG report. Secondly the primary benefit of using hazard ratios is that they account for the biases introduced into the probabilistic results and the characterisation of uncertainty around these results. Presenting only new deterministic point estimates with hazard ratio values incorrectly substituted as relative risks, as the manufacturer has done in their response, is both misleading and entirely misses the point of the ERG's concern.

It is important to note that all numbers presented are in the context of a model which the ERG has demonstrated to be very sensitive to changes in assumptions and data (see section 6 of the ERG report). The ERG feels that the new analyses presented by the manufacturer as a response to the ACD do not resolve these uncertainties, and do not attempt to tackle the key issues highlighted in the ERG report. Non-linear models must be evaluated probabilistically and a fully incremental analysis should be carried out against all relevant comparators (including those listed in the NICE scope) in a

meaningful population to get a meaningful understanding of the likelihood that a technology is cost-effective.

The ERG do not feel any new facts have been presented to challenge the comments made in the ERG report with respect to the effectiveness and cost-effectiveness of fingolimod. The manufacturer's response represents a difference of opinion on these issues. Where the manufacturer has tried to quantitatively address some of the minor criticisms made by the ERG (see discussion of points D3 and D6 above), they have demonstrated that the ICER increases by accounting for these issues. With respect to points D7 and D9 the manufacturer has not actually addressed the issues that have been highlighted by the ERG.