CRD and CHE Technology Assessment Group

Fingolimod for the treatment of relapsing remitting multiple sclerosis

27th January 2012

ERG Discussion of Manufacturer's Response to Second ACD

The manufacturer has submitted a response dated 5th January 2012 to the document: Fingolimod for the treatment of relapsing remitting multiple sclerosis (RRMS) – Second Appraisal Consultation Document (ACD) produced by NICE. The ERG was requested by the Institute to provide additional commentary and validity checks on the comments provided by the manufacturer on this second ACD. 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 five sections A-E and comes with an associated revised model that was used to generate the results in the response. In the following paragraphs we will deal with each of these sections in turn summarising the issues dealt with in each section and verifying whether or not we were able to reproduce the presented results using the submitted revised model.

Section A deals with innovation, no new results are presented in this section.

Section B deals with the committee's assumption in the second ACD that one third of sub-optimal responder population receive best supportive care (BSC). The manufacturer has collected some data to suggest that this proportion is higher than observed in clinical practise. The ERG has no means to verify this data. The ERG's clinical advisor commented on the definitions of the disease states in the survey and how these match the population in the license. These comments are reported at the end of this document.

Section C presents Prescriptions Pricing Authority proportions of different interferon beta prescribed between 2008 and 2010. The ERG has no means to verify this data.

Sections B and C aim to inform an analysis introduced by the committee, where the costs and effects of a range of alternative treatments are combined using the proportions used in clinical practice to create a 'blended' comparator to fingolimod. The ERG urges caution in using this blended comparator approach – previous NICE deliberation on the use of this approach concluded that a fully incremental analysis was the appropriate way to handle the issue of multiple comparators (see the NICE final appraisal determination for Lapatinib 3.29-3.30 and 4.14 http://www.nice.org.uk/nicemedia/live/11731/49197/49197.pdf) and the ERG supports this view.

Section D describes the manufacturer's revised base case results. The ERG note that all analyses referred to population 1b, rather than population 1b not 2. The issues around the adequacy of population 1b have been presented by the ERG (see ERG report sections 3.1, 5.2.2 and 6.2) and discussed previously by the committee.

The revisions made by the manufacturer to the model are:

1) Incorporated trial EQ-5D data for utilities in EDSS states 0 to 6

   The manufacturer justifies this change as a response to a request by the committee. The ERG has previously explored alternative ways to do this in the ERG report (see ERG report section 6.7).

2) Added the assumption that there is a 50% waning of treatment effect after 5 years.

Given the second ACD has commented on the extrapolation assumption undertaken in the initial analyses submitted, the manufacturer introduces a waning of the treatment effect in this revised model. To justify the timing and extent of the waning, the manufacturer presents evidence from an extension to the FREEDOMS trial – the data presented show that [redacted]; however, these data relate to treatment effect on relapse rates, rather than on progression, the latter being the key effectiveness driver in the model. Data on observed treatment effects beyond 4 years have not been presented. These data are unpublished, and as a consequence the ERG was unable to verify this evidence. Alternative assumptions over the extrapolation of treatment effects have been previously explored by the ERG (see ERG report section 6.7).

3) Updated administration costs of the different treatments

The ERG has successfully verified that the stated changes were made in the revised model which the manufacturer submitted. No attempt has been made by the ERG to assess the validity of the new assumptions.

The manufacturer has used this revised model to calculate probabilistic cost-effectiveness results separately for interferon beta-1a (im), i.e. Avonex, and interferon beta-1a (sc), i.e. Rebif 44. These were each calculated relative to fingolimod. The ERG has run the updated model and was able to successfully approximate the cost-effectiveness results for these two comparators presented in table 3 and table 4 in the manufacturer's response.

It should be noted that for probabilistic results to be strictly comparable they should be simultaneously computed from the same probabilistic sensitivity analysis (PSA). The results obtained by the manufacturer have been computed independently, and due care should be taken when interpreting these numbers. Additionally, the ERG has previously noted a numbers of issues in the way the PSA is implemented in the model (in response to the manufacturer's initial submission, see ERG report section 5.2.10 for a full discussion); it should be noted that the current model has not addressed any of these issues. For these reasons the ERG would urge caution in interpreting these results.

An additional comparator, interferon beta-1b i.e. Betaferon, is then introduced in the analysis. It is important to note that the ERG has not previously critiqued any of the analysis around this. Due to problems with the model file supplied by the manufacturer, the ERG was not able to run a probabilistic analysis for this new comparator in the model -- it was thus not possible to verify the results in table 6 for the weighted mean ICER (blended comparator). Running the deterministic analysis for Betaferon produced significantly different results than those reported in the manufacturer's response (the reported results were presumed to be taken from a probabilistic analysis).

Additionally the results reported in table 6 for BSC suggest a significantly worse response under BSC than the ERG has been able to reproduce using either probabilistic or deterministic runs of the model.

In summary, the ERG is able to verify that the new assumptions have been implemented in the model and that using this revised model the ERG have been able to replicate the new probabilistic cost-effectiveness results for fingolimod against Avonex and for fingolimod against Rebif 44

separately. The ERG was not however able to replicate the cost-effectiveness results for Betaferon as the submitted model file does not seem to contain the required data to do so. Also, the ERG was not able to replicate the results for BSC as the model as run by the ERG produced significantly different results to those presented in the manufacturer's response. The ERG was therefore not able to verify the weighted mean ICER as the constituent results could not be reproduced from the submitted model.

Section E describes a scenario where the model is run with an alternative structural assumption around natural history disease progression. It is important to note that the results presented in this section are stated to be specifically for the unrevised model, looking at a comparison between fingolimod and interferon beta-1a (im) i.e. Avonex. These are not comparable to the results presented in the previous section for the revised model and the blended comparator.

The file supplied by the manufacturer did not allow the ERG to compute this new scenario in an automated way; hence it has not been possible for the ERG to verify these results within the required timeframe. The ERG has previously submitted analysis investigating a range of alternative assumptions around natural history progression rates (see ERG report section 6.5).

ERG Summary

The ERG feels that all the issues highlighted in the original ERG report and the subsequent ERG submissions still apply. The concerns around the robustness of the model, the arbitrary nature of the assumptions and the absence of a fully incremental analysis remain pertinent. Any predictions from the model should be seen in light of these concerns.

The ERG also urges caution in using a blended comparator approach – previous NICE deliberation on the use of this approach concluded that a fully incremental analysis was a more appropriate way to handle the issue of multiple comparators (see the NICE final appraisal determination for Lapatinib 3.29-3.30 and 4.14 http://www.nice.org.uk/nicemedia/live/11731/49197/49197.pdf) and the ERG supports this view.

ERG Clinical advisor comments on definitions of disease states in survey

- *Question 2 in survey - This is population 2 with Rapidly evolving severe RRMS (RES) with 2 disabling relapses in 1 year and with a new lesion on MRI.*

- *Question 3 in survey - This meets the clinical criteria for population 1a but not the MRI criteria. 1 relapse only in previous year. No indication of MRI findings. Could meet criteria for 1b if pre-treatment relapse rate was 1/year. ie unchanged for current year but not if higher pre-treatment relapse rate.*

- *Question 5 in survey - This meets criteria for population 1b if the pre-treatment relapse rate was 1 relapse/year ie unchanged relapse rate. If pre-treatment relapse rate was 2/year then relapse rate would have improved. Response to this question is dependent on pre-treatment relapse rate which was not given.*