National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Fingolimod for the treatment of relapsing-remitting multiple sclerosis

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from the NHS Centre for Reviews and Dissemination and Centre for Health Economics, University of York to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 5pm, **17 June 2011**, using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The attached proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Inaccurate representation of content of manufacturer submission with regards to the relative risk of Avonex vs. placebo in Population 1b

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 13 it states: "This is supported by the fact that the ARR for the Avonex group in TRANSFORMS was 0.506 while that for the placebo arm of FREEDOMS was 0.542." This sentence does not support the preceding sentence. Avonex has a lower ARR than placebo demonstrating it is more effective not less effective than placebo.	The entire sentence and point needs to be removed	The argument made by the ERG is flawed and unsubstantiated.	The ERG does not consider that this is a factual inaccuracy. However this point has been clarified to emphasise that the ARR versus placebo is similar to (as opposed to lower than) that versus Avonex, indicating low efficacy of Avonex in this population. The ERG report now reads as follows (p13): "*This is supported by the fact that the ARR for the Avonex group in TRANSFORMS was 0.506 while that for the placebo arm of FREEDOMS was 0.542; the difference between these rates is small indicating that the benefit over BSC conferred by Avonex may be limited.*"

Issue 2 Further inaccurate representation of content of manufacturer submission with regards to the relative risk of Avonex vs. placebo in Population 1b

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 13 it states: "Indeed the indirect comparison	The entire sentence and point needs to be removed from pages 13, 16, and page 41	Neither of the RR's used in the base case analysis suggests that Avonex	The ERG accepts this point and have amended the ERG report accordingly. This

used in the economic model indicates that Avonex has negative utility and is <u>less beneficial than placebo.</u> This in itself is indicative of the fact that it represents a non-ideal comparator in the base-case population." In the model the relative risk (RR) of 3-month progression for Avonex vs. placebo in the base case was [redacted]. And the RR of relapse of Avonex vs. placebo was 0.933. This factual inaccuracy is also restated on pages 16 and 41.		was worse than placebo. This means that these statements by the ERG are incorrect and need to be removed.	statement has been changed to reflect the fact that, while it is only for population 1b but not 2 that the indirect comparison shows negative utility of Avonex, Avonex is nonetheless dominated or extendedly dominated by BSC in both populations and is less cost-effective in population 1b than population 1b but not 2. The ERG report now reads as follows (p13): "*Indeed the indirect comparison used in the economic model indicates that Avonex has negative utility in population 1b but not 2, and is less beneficial than placebo. This is also indicative of the fact that it represents a non-ideal comparator*." On p16 the ERG report now reads as follows: "*This is particularly the case given that the indirect comparison for population 1b but not 2 indicates that Avonex may be less beneficial than placebo, while*

			Avonex is dominated or extendedly dominated in both populations 1b and 1b but not 2 (and is less cost-effective in population 1b than in population 1b but not 2)" *On p41 the ERG report now reads as follows:* *"Given that the indirect comparison presented for population 1b but not 2 indicated Avonex to be less cost-effective than placebo, while Avonex was dominated or extendedly dominated for both populations 1b and 1b but not 2, the appropriateness of this is clearly open to question."*

Issue 3 Misunderstanding by the ERG to understand why "Population 1b minus 2" reduces the cost-effectiveness compared to "Population 1b"

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 20 it states:"... the fact that exploration of the model revealed significant differences in the cost effectiveness of fingolimod in the two populations suggests that it is highly sensitive	Page 20 should read: "...the fact that exploration of the model revealed significant differences in the cost effectiveness of fingolimod in the two populations demonstrates that it is sensitive to changes in disease	This failure by the ERG to understand what the impact of disease progression can be has led the ERG to incorrectly believe there most be something wrong with the	The ERG are drawing attention to the fact that, not only is the model highly sensitive to changes in parameters, but also that the methods used to calculate the parameters are

to small changes in parameters." The difference in cost-effectiveness is largely due to the change in relative risk of 3-month disability progression of Avonex vs. placebo changing from [redacted] to [redacted]. This is a change of [redacted]. Novartis don't believe this is a small change. The model is modelling the progression of disease. So it is not a surprise that a change in [redacted] of the relative risk of disease progression of Avonex vs. placebo would result in a dramatic change in the cost-effectives of fingolimod vs. Avonex.	progression."	robustness of the model.	also highly sensitive to changes in their input data i.e. the small change in patient population leading to large swings in parameter values. The sentence in the ERG report has been amended to reads as follows (p20): *"... the fact that exploration of the model revealed significant differences in the cost effectiveness of fingolimod in the two populations suggests that it is highly sensitive to changes in parameters, and that these parameters in turn are highly sensitive to minor changes in the patient population."*

Issue 4 Misunderstanding by the ERG of the systematic review methodology relating to identification of cost effectiveness studies.

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 46 the ERG claims that the systematic review did not include non-fingolimod cost-	Novartis believes the statement made by the ERG on page 46 is plainly wrong and highly misleading. This sentence needs changing to:	Section 6.2.3 (Page 198) of the submission clearly states that the Novartis fingolimod model was heavily influenced by the existing	The ERG does not consider that this is a factual inaccuracy.

effectiveness studies. Section 6 and Appendix 9.10 of the Novartis submission clearly state this is not true.	"No references met the primary aim of the search to identify an existing cost-effectiveness model of fingolimod. So the manufacturer decided to develop a de-novo fingolimod model based on the literature. From the systematic review two cost-effectiveness models had been identified which closely matched the criteria described in the NICE scope for the fingolimod STA. These models were: (1) The model developed by ScHARR for the interferon and glatiramer acetate MTA. (2) The model developed by Biogen for the STA of natalizumab. The second model was heavily based on the model developed by ScHARR. The literature about these models was a useful source of information for the fingolimod model structure and many of the key assumptions underpinning the Novartis fingolimod model. "	Biogen Natalizumab STA model and the ScHARR DMT model. A comparison of the structure and many of the inputs from the three models clearly demonstrates a large overlap between them. It is unacceptable to suggest that Novartis did not review the existing literature systematically. This misunderstanding by the ERG was not raised as an issue by the ERG during the clarification questions, so Novartis has not been able to address this matter prior to the ERG report being produced. This is unfortunate because it has led to a number of misunderstandings by the ERG. These additional issues are discussed below.	The manufacturer's submission clearly states (pg 190) that "The primary objective of this review was to systematically search and identify all existing economic evaluations of fingolimod for the treatment of adults with RRMS". Also, the inclusion criteria and exclusion (p191) clearly states that the intervention of interest is fingolimod and that other interventions were excluded.

Issue 5 Misunderstanding and speculation by the ERG of the synthesis of evidence on outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 49 it states: "Although a systematic review on treatment effectiveness measures and a mixed treatment comparisons (MTC) were conducted, these results were not used to inform cost-effectiveness. Instead a separate, indirect analysis relying on specific trials, FREEDOMS and	Novartis believes these speculative statements by the ERG are wholly inaccurate and misleading and need to be removed from the report. This paragraph on page 49 should read: "A systematic review on treatment effectiveness measures was conducted. A mixed treatment comparisons (MTC) were conducted but these results were not used to inform cost-	All of the inputs in the model were identified using a systematic review which is extensively detailed in the submission. The selection of the two trials for the efficacy inputs for the model is discussed in great depth in Section 6 of the submission.	The ERG does not consider the statement on page 22 to be a factual inaccuracy. The submission does not mention literature reviews on parameters such as natural history progression, relapse, conversion or mortality. Thus we do not believe the

TRANSFORMS, was used. The search for evidence on other input parameters did not appear to be based on a systematic process." On page 22 is also states: "These were combined in an MTC; however this was not subsequently used to inform the economic model, which therefore rests on the comparison with Avonex." Novartis would like to highlight that all the inputs into the model were identified using a systematic review which is extensively detailed in the submission. The selection of these two trials is discussed in great depth in Section 6 of the submission.	effectiveness because they were for the RRMS population. Instead a separate, indirect analysis relying on specific trials, FREEDOMS and TRANSFORMS, was used because there are the only trials for which data for the Population 1b was available to Novartis." On page 22 is should state: "These were combined in an MTC; however this was not subsequently used to inform the economic model <u>because they are for RRMS and not Population 1b</u>."		statement on p49 of the ERG report is factually inaccurate. Nevertheless, for clarity, we have modified this statement, as follows: *"The search for evidence on many other input parameters did not appear to be based on a systematic process."*

Issue 6 Unsubstantiated speculation by the ERG regarding the search strategy for clinical evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 22 it states:"Due to issues with the reported search strategy (see section 4.1.1 below) " A review of Section 4.1.1 (page 25) for these issues found the following comment:	These statements on pages 22 and 25 need to be removed from the report.	The claims about "inappropriate elements" and "non-ideal construction" are unsubstantiated and wrong. The discussion of a "non-RCTs" filter is plainly incorrect.	The ERG does not consider these to be factual inaccuracies but is happy to detail instances of inappropriate elements in the search strategy; these were excluded in the previous version of the ERG report for

"Whilst there were some inappropriate elements in the search strategies used, and relevant material may have been missed as a consequence, the ERG did not identify any relevant studies which were not identified by the manufacturer's search. The search for clinical evidence may therefore be considered fit for purpose despite its non-ideal construction. However, these alleged inappropriate elements are not actually detailed in the ERG report. Page 25 goes on to states: *"As the searches for adverse events data, the MTC and non-RCT evidence employed the same strategy, they may also be considered fit for purpose, with the additional caveat that the use of a filter in the search for non-RCTs may have contributed to relevant material being missed."* However, Appendix 9.2 of the submission details the systematic review and it can be clearly seen there was no filter for "non-RCTs".			reasons of brevity and because the search was considered to be overall fit for purpose. The ERG report now reads as follows (p25): "*There were some inappropriate elements in the search strategies used, such as the use of a facet to search the Cochrane Library for RCTs and use of economic studies search terms for NHS EED (these are inappropriate due to the content of the respective databases), and relevant material may have been missed as a consequence. However, the ERG did not identify any relevant studies which were not identified by the manufacturer's search."* A filter for both RCTs and non-RCTs was used; this is clear from tables 93 and 94 in the manufacturer's submission. The ERG report has been changed slightly to clarify this and now reads (p2?): *As the searches for adverse events data, the MTC and non-RCT evidence employed the same strategy, they may also*

			be considered fit for purpose, with the additional caveat that the use of a filter for both RCTs and non-RCTs (detailed in Tables 93 and 94 in the manufacturer's submission) may have contributed to relevant material being missed.

Issue 7 Misunderstanding by the ERG of the selection of EDSS baseline distribution for the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 52 the it states: *"The submission presents data on the distribution of patients across EDSS states for several different MS studies (shown in Figure 2). The figure confirms that the subgroup of patients analysed from the FREEDOMS and TRANSFORMS trials have lower EDSS scores than those seen in the other studies. <u>This suggests that the trial samples (used further in the model) may not be representative of the non-responder population within routine clinical practice.</u> This has not been adequately discussed or addressed in the manufacturer's submission"*	On page 52 all of the discussion about the inappropriateness of the EDSS distribution should be removed. The comments on pages 14 should be removed.	The discussion is based on a misunderstanding by the ERG and does not accurately reflect the Novartis submission. Novartis disagrees with the ERG that it is automatically correct to use the EDSS distribution from a general RRMS population instead of Population 1b specifically. In addition, the use of this argument on page 14 as a means to imply the rest of the Novartis submission is inappropriate is unsubstantiated.	The ERG does not consider that this issue represents a factual inaccuracy. The ERG has not made any claims on what is or is not correct to use in the model; specifically, the ERG has not stated that the EDSS distributions used in the model are inappropriate. The point being made by the ERG is that it is important that the choices made by the manufacturer regarding alternative sources of data should be appropriately justified and that the generalisability of results to routine clinical practice in the NHS and the potential

The reason the baseline EDSS distribution for the model was taken from the trials FREEDOMS and TRANSFORMS is because the model is modelling the specific population 1b. Novartis carried out a systematic review to identify potential sources for the base line EDSS distribution. All of these sources are discussed in the submission and are in Figure 2 of the ERG report. The problem with the London Ontario, the UK RSS, and the US MS survey data is that they are all for a general RRMS population and NOT Population 1b specifically. Novartis believed it to be more robust and fitting with the NICE reference case to use data specifically for Population 1b where available since this would match the population being modelled. If the ERG disagreed with the rationale they should have raised this during the ERG clarification questions as per the NICE process.			robustness of the cost-effectiveness results should be adequately considered.

Issue 8 Misunderstanding by the ERG of the selection of the HRQoL data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5.2.7 (Page 76) states "While EQ-5D data on patient utility was collected as part of the trials, this was not used within the economic model. Instead, the manufacturer used external literature to estimate the relationship between EDSS scores and EQ-5D. No justification was given for choosing external literature in favour of the trial data and, while several external studies were identified, the choice of the Orme et al (2007) study from those identified was not justified." This assertion is repeated on pages 95, 111 and 113. It is also the basis of the ERG's exploratory analysis in Section 6.7 The Novartis systematic review identified four utility sources for MS by EDSS (see Table 59 of the submission). Full details of the selection of Orme 2007 is given in Appendix 10 of the submission.	Section 5.2.7 (Page 76) should state: "While EQ-5D data on patient utility was collected as part of the trials, this was not used within the economic model. Instead, the manufacturer used external peer-reviewed literature to estimate the relationship between EDSS scores and EQ-5D. Justification was given in Appendix 10 for choosing external literature in favour of the other studies and the trial data." On page 95 it should say: "Many alternative external HRQL data sources are available the choice of Orme was due to the lack of complete data for some of the EDSS states and SPMS patients." On page 111 the sentence "*The utility estimates used in the manufacturer's base case appear to be selected arbitrarily and the impact on model results of using alternative utility values has not been investigated."* needs removing. On page 113 the sentence "While the model is highly sensitive to small changes in these values, there is no clear justification for the utility data selected by the manufacturer" needs removing.	The claims by the ERG are incorrect and misleading. Appendix 10 of the submission details this selection of HRQoL data. But briefly the explanation is: Four published studies were identified. Parkin 1998 was rejected because it does not report utilities for the complete set of EDSS states. The Orme 2007 study and the Biogen 2007 study is the same data set but with different methods of combining the EDSS half states (0.5, 1.5, 2.5 etc). Orme 2007 was preferred because this has been peer reviewed; however the differences in the reported utility between the Orme 2007 and Biogen 2007 are small. The fourth source were utilities reported by the ERG in NICE TA 127. These were taken from the original ScHARR model report. However, the methodology of obtaining theses utility scores is not described so this raised some substantial doubt. The EQ5D data from the trials FREEDOMS and TRANSFORMS was considered, but there were a number of caveats which lead Novartis to believe the Orme 2007	The ERG does not consider that this issue represents a factual inaccuracy. Appendix 10 of the manufacturer's submission does not detail: (1) The actual results (as opposed to the number of matches) found from the searches conducted; (2) the criteria used to justify the use of external data in preference to the trial data; or (3) the criteria used to select between the external sources of utility data for use in the model.

		data to be the more appropriate even when the concerns of PenTAG in TA 127 were considered. The caveats were: (1) Due to the entry criteria, at baseline there was only EQ5D data for EDSS states 0 to 5.5. (2) The study excluded SPMS patients. (3) At the end of the study few subjects had progressed beyond EDSS 7 so the trial end data was of limited use for the model. (4) Extension data for FREEDOMS and TRANSFORMS which includes more subjects with EDSS states higher than 7 was not available at the time of submission in March 2011. Novartis considered combining all the results in a meta-analysis but rejected this due to the heterogeneity between the studies. Novartis are unclear why this issue of not understanding the selection was not raised by the ERG during the clarification questions. If it had been brought up the matter could have been discussed before the	

		misunderstanding became incorporated into the ERG report.	

Issue 9 Further misunderstanding by the ERG of the selection of HRQoL data for the 10 EDSS states

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 78 it repeats the misunderstanding about the selection of HRQoL data from page 76 but it further goes on to say: "*The ERG considers that since the submission targets a very specific patient subgroup, it would have been appropriate to use HRQoL data for this same subgroup available directly from the trials."*	This should read: "The ERG considers that since the submission targets a very specific patient subgroup, it would have been appropriate to use HRQoL data for this same subgroup available directly from the trials. However, since there is limited trial utility data for subjects with SPMS and/or are in EDSS states beyond 7 the data would be limited. "	The reason for not using specific utility data from Population 1b is because there is limited utility data from the trials for patients beyond EDSS or who have SPMS.	It is explicit that the statement made on p76 refers to the ERG's opinion on this matter: The ERG does not consider there is any factual inaccuracy in the statements made.

Issue 10 Further misunderstanding by the ERG of the selection of HRQoL data for the 10 EDSS states

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 111 it also repeats the ERG's misunderstanding about the HRQoL data. Here it states: "*There were a number of challenges involved in using this trial data: the manufacturer only provided values for patients in RRMS states, and only for patients in EDSS states 0*	The sentence on Page 111 should read: "There were a number of challenges involved in using this trial data: the trial entry requirements excluded non RRMS patients and patients with an EDSS state greater than 5.5"	The ERG has misunderstood the limited nature of the HRQoL trial data. In addition, they have misunderstood why the Orme 2007 HRQoL data was used. This misunderstanding could have been addressed during the ERG	The ERG does not consider that this issue represents a factual inaccuracy.

to 6” The trials excluded subjects with SPMS or an EDSS greater than 5.5. This was one of the main challenges in using the trial HRQoL data in the model and was a major reason why the trial data was not used in the model.		clarification questions.	

Issue 11 Misunderstanding by the ERG of the selection of the natural history matrices

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 61 it states: “There does not appear to have been a systematic approach to searching for evidence to describe the natural history.” All of the inputs into the model were identified by a systematic review which is extensively described in the submission.	The sentence needs removing	The sentence is factually incorrect and does not accurately reflect the Novartis submission.	The ERG does not consider there is any factual inaccuracy in the statements made. The submission does not mention systematic literature reviews on parameters such as natural history progression, relapse, conversion or mortality. See response to Issue 5.

Issue 12 Misunderstanding by the ERG of the justification of the natural history matrices

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 61 it states: *“Despite previous models in MS having utilised the same dataset, no attempt was made in the*	The sentence on page 61 should be removed.	The sentence in the ERG report makes no logical sense. In addition, the second half of the sentence implies there is other potential	The ERG does not consider there is any factual inaccuracy in the statements made.

submission to justify the use of this particular study over either the control arm of the FREEDOMS trial or any other potential external studies." The reason the FREEDOMS and TRANSFORMS trials were rejected is because they only recruited RRMS patients with an EDSS of 5.5 or less. Basing the natural history on just this data set would severely limit model. It would also raise the question of what data to use for SPMS or patients with an EDSS greater than 5.5.		external studies but doesn't substantiate this claim. This could have been dealt with in the ERG clarification questions.	See response to Issue 5.

Issue 13 Misunderstanding by the ERG of the derivation of the natural history matrices

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 61 it states: "*No attempt was reported in the manufacturer's submission to internally validate the transition matrices used in the model against the trial data or to externally validate these matrices against other published natural history datasets."* The FREEDOMS and TRANSFORMS trials were only recruited RRMS patients with an	On page 61 it should state: "The manufacturer was unable to internally validate the transition matrices used in the model against the trial data or to externally validate these matrices against other published natural history datasets because there is a lack of data available."	The sentence in the ERG report makes no logical sense. In addition, the last part of the sentence implies there are other potential external studies but the ERG don't substantiate this claim.	The ERG does not consider there is any factual inaccuracy in the statement made.

EDSS of 5.5 or less. Comparing the natural history to this would raise the question of what data to use for SPMS or patients with an EDSS greater than 5.5.			

Issue 14 Misunderstanding by the ERG of the selection of the data to inform the calculation of the natural history matrices

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 65 it states: "The manufacturer has not reported having conducted literature searches (systematic or not) to find evidence on conversion and has not presented any justification for using this dataset." All of the inputs into the model were identified by a systematic review. In this search Novartis were unable to identify an alternative source other than the sources used in the STA of natalizumab and the MTA of DMTs. So the natural history transition calculations were taken from these previous appraisals.	Page 65 should state: "The manufacturer was unable to find additional evidence on conversion and so has used the same methodology as the previous NICE appraisals for natalizumab and the DMTs."	The sentence in the ERG report is factually incorrect.	The ERG does not consider there is any factual inaccuracy in the statements made. The submission does not mention systematic literature reviews on parameters such as natural history progression, relapse, conversion or mortality. See response to Issue 5.

Issue 15 Further misunderstanding by the ERG of the selection of the data to inform the calculation of the natural history matrices

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 65 it then states: It is difficult to assess the validity of these results as there is no attempt by the manufacturer to validate the calculated SPMS conversion rates either internally against trial observations or externally against other published studies. In addition the manufacturer has not reported any conversion data from the FREEDOMS and TRANSFORMS trials for the ERG to be able to carry out its own internal validity assessment." The FREEDOMS and TRANSFORMS trials only recruited RRMS patients with and EDSS of 5.5 or less. In addition, the SPMS conversion rate was not reported in the trials.	The two sentences should be removed.	The sentence in the ERG report makes no logical sense. In addition, the first part of the sentence implies there are other potential external studies, but the ERG doesn't substantiate this claim.	The ERG does not consider there is any factual inaccuracy in the statements made. The submission does not mention that systematic literature reviews were used to identify evidence on natural history parameters such as progression, relapse, conversion or mortality. See response to Issue 5.

Issue 16 Further misunderstandings by the ERG of the selection of the data to inform the calculation of the natural history matrices

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 67 it states:	The sentence should be removed.	The sentence in the ERG report is	The ERG does not consider

"There does not seem to have been any systematic search for studies on relapse rates and no justification is provided for the studies selected to calculate the natural history values. " All of the inputs into the model were identified by a systematic review. The review did not identify other sources more suitable than the analysis from the previous NICE STA of natalizumab and the MTA of DMTs.		factually incorrect.	there is any factual inaccuracy in the statements made. The submission does not mention that systematic literature reviews were used to identify evidence on natural history parameters such as progression, relapse conversion or mortality. See response to Issue 5.

Issue 17 Further misunderstandings by the ERG of the selection of the data to inform the calculation of the natural history matrices

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 67 it states: "External data is used to describe both the MS patient population distribution and the relapse rates they experience in favour of trial data. No attempt to assess external validity of these relapse rates was made." The FREEDOMS and TRANSFORMS trials only recruited RRMS patients with and EDSS of 5.5 or less. This means	The sentence should be removed	The sentence in the ERG report is wrong. The external data was used in favour of the trial data. It was used because there is limited trial data for SPMS patients and/or patients with an EDSS of 6 or more.	The ERG does not consider there is any factual inaccuracy in the statements made.

there is limited trial data for SPMS patients and/or patients with an EDSS of 5.5 or more. This means any comparison could only focus on RRMS patients with an EDSS of 5.5 and less.			

Issue 18 Further misunderstandings by the ERG of the selection of the data for the natural history of the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 94 it states: "Trial data largely ignored - used neither in the model natural history nor to validate model natural history inputs." This is incorrect. The model used trial data where possible. As discussed above, the trial data was not used for the natural history transition matrices or natural history relapse rates because the trials excluded patients with an EDSS over 5.5 and/or SPMS.	The sentence should be changed to: "Trial data was used where possible, but was not suitable for the natural history matrices or the natural history relapse rates."	The sentence in the ERG report is incorrect and not an accurate reflection of the Novartis submission. The use of the word "ignored" implies that the data was deliberately overlooked as opposed to the truth which is that the data was unsuitable.	The ERG does not consider there is any factual inaccuracy in the statements made.

Issue 19 Misunderstanding by the ERG of the identification, selection, and derivation of key parameters in the model - summary

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On pages 14, 93 and 114 the ERG contains a summary stating	These paragraphs on pages 14, 93, and 114	These statements by the ERG are factually incorrect and do not reflect	The ERG does not consider there is any factual inaccuracy

that the manufacturer does not appear to have used a systematic approach to identify and select appropriate data sources to inform the key parameters of the model – choices of data appear to be arbitrary and unjustified. It also states "Methods used for subsequently deriving the various model parameters from the selected data are not fully described and assumptions made in using these methods are not discussed or justified." (Page 114) As discussed above for each of the variables discussed in depth in the ERG report the literature sources for the variables were identified by a systematic review. The selection of each of the variables is discussed above.	need to be removed from the report.	the submission. It concerns Novartis that none of these misunderstandings about the systematic reviews were raised during any of the clarification questions from the ERG.	in the statements made. See ERG's responses to the issues above.

Issue 20 Misleading statement by the ERG of which HRQoL parameters were incorporated into the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 48 it states: *"In addition, disutility from treatment was considered for Avonex only. Fingolimod was assumed to have no treatment disutility as an oral drug."*	The paragraph on page 48 should read: "In addition, disutility from treatment administration was considered for Avonex only. Fingolimod was assumed to have no treatment administration disutility as it is an oral drug."	The sentence is factually incorrect and misleading.	The ERG does not consider there is any factual inaccuracy in the statements made. This is stated in section 6.4.15 in the manufacturer's

This is misleading. Disutility due to administration of fingolimod was not incorporated because it is an oral capsule and so avoids the disutility associated with an injection. But, importantly, the model did incorporate the disutility due to side effects due to fingolimod. Table 63 of the submission details the disutility due to fingolimod side effects.			submission

Issue 21 Misunderstanding about the input data used in the model regarding treatment discontinuation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 74 states: *"The data on discontinuations due to AEs are obtained from the head-to-head trial; however, the discontinuation data for the whole trial population are applied rather than for the subset of interest (population 1b)."* The model uses discontinuation data from the subset Population 1b. This is documented in Table 58 (Pg 219) of the submission. This misunderstanding by the ERG is also repeated on page 76. We also believe it's repeated on	Page 74 should state: "The data on discontinuations due to AEs are obtained from the head-to-head trial from the subset of interest (population 1b)." On page 76 the following sentence should be removed: "Finally the use of the whole trial population for some model inputs e.g. discontinuation data, whilst using more severe subsets of the trial population for other model inputs, e.g. treatment effects, is not discussed or justified."	The sentences are all factually incorrect	The ERG does not consider there is any factual inaccuracy in the statements made. This is stated in the final paragraph of Section 6.3.1 of the manufacturer's submission.

page 95 where it says: “Inconsistent use of trial data where subsets are selectively used”.	The sentence on page 95 should be removed or clarified.		

Issue 22 Unsubstantiated claim by the ERG to have been selective with data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 76 states: “Overall, the selective use of data, the lack of validity assessment of results, the unjustified treatment effect extrapolation assumptions and the incorrect usage of relative risks in place of hazard ratios together indicate a high degree of uncertainty around model predictions.” There is no evidence presented in the preceding discussion that Novartis has been selective with data.	The sentence needs to be removed.	The sentence is factually incorrect and unsubstantiated.	The ERG does not consider there is any factual inaccuracy in the statements made. See ERG’s responses to the issues above.

Issue 23 Misunderstanding by the ERG about the available data for Population 1b

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 76 also states: “Additionally, exploring the wider network of evidence suggests that there may be other more	This sentence should be removed	The sentence is factually incorrect and misleading.	The ERG does not consider there is any factual inaccuracy in the statements made.

appropriate comparators than Avonex that should have been considered by the manufacturer". As discussed in previous issues and in the submission, other comparators were considered but Novartis was unable to identify any other data in the population of interest.			

Issue 24 Unsubstantiated claim by the ERG about the selection of effectiveness data for Population 1b

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 95 states: "*Much of the available evidence that could have been used to inform effectiveness estimates is ignored. Only the FREEDOMS and TRANSFORMS trials are included".* As discussed in previous issues and in the submission, all of the trials identified in the systematic review were considered. Only FREEDOMS and TRANSFORMS contained data for population 1b	This sentence should be changed to: "Much of the available evidence to inform effectiveness estimates was not suitable because it was not for Population 1b. Only the FREEDOMS and TRANSFORMS trials are included".	The sentence is misleading, unsubstantiated and inaccurate. The use of the word "ignored" implies that the data was deliberately overlooked as opposed to the truth which is that the data was unsuitable.	The ERG does not consider there is any factual inaccuracy in the statements made.

Issue 25 Misunderstanding by the ERG of the licensed population for fingolimod

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 85 the ERG states: *"Effectiveness estimates for Avonex are derived from an indirect comparison using the FREEDOMS and TRANSFORMS studies; however, the manufacturer's submission refers to the MSCRG trial directly comparing Avonex to placebo which has not been used to inform the effectiveness estimates. There are also a number of other studies referenced that directly compare fingolimod or Avonex to other comparators – these could also be informative as part of a network."* Section 5.6 has a detailed discussion about potential networks and Novartis constructed several. The liming factor was that all of these networks are for RRMS patients. Novartis attempted to construct a network for Population 1b which is a subpopulation of RRMS, but could only identify FREEDOMS and TRANSFORMS as potential data sources.	The sentence on page 85 should be truncated to: "Effectiveness estimates for Avonex are derived from an indirect comparison using the FREEDOMS and TRANSFORMS studies."	The sentence is illogical since it ignores the lack of data available to construct such a network.	The ERG does not consider there is any factual inaccuracy in the statements made.

Issue 26 Unsubstantiated speculation by the ERG about the accuracy of the natalizumab infusion cost

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 85 the ERG reports that Novartis has found that the NHS tariff code A18 has been superseded by code AA30Z in the 2010/2011 tariff. The ERG then goes on to speculate if this is actually correct without providing any contrary evidence. The ERG then use this unsubstantiated speculation as a means to discredit the analysis by Novartis.	The entire paragraph on page 84 and 85 which starts: "*The ERG would like to raise their concern...*" needs to be removed.	The 2010/2011 NHS tariff is clear that tariff code A18 has been superseded by code AA30Z. This means when a 2010 perspective is taken of the NICE costing template for natalizumab that the logical step is to use the equivalent 2010 cost from the 2010/2011 tariff. The 2010/2011 tariff details what cost the NHS will charge for this procedure. If the ERG disagrees with the 2010/2011 tariff then it needs to provide evidence and not just speculate.	The ERG does not consider there is any factual inaccuracy in the statements made. The ERG raised its concerns over the significant difference between the administrative cost associated with natalizumab in the report and in the NICE costing guidance.

Issue 27 Inaccurate representation of content of manufacturer submission with regards to the monitoring required for fingolimod

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On Page 85 the ERG includes a discussion of the administration and monitoring costs of fingolimod. As part of this discussion it states: "The requirement for these additional tests appears to be	This sentence on page 85 should read: "The requirement for these additional tests is based on the SPC for fingolimod. The frequency of patients who need any additional resources associated with the SPC requirements is taken from FREEDOMS"	The sentence is incorrect. The SPC is clear what tests and monitoring is required for fingolimod.	The ERG has amended the report accordingly. The ERG report now reads (p85): "*The requirement for these additional tests is based on the SPC for fingolimod. The*

based on results collected during the FREEDOMS trial."			*frequency of patients who need any additional resources associated with the SPC requirements is taken from FREEDOMS"*

Issue 28 Inaccurate representation of content of manufacturer submission with regards to the monitoring required for comparator therapies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 86 it discusses why Avonex requires four neurological visits. The reference for this is the ABN guidelines which states that for the injectable DMTs four neurology visits are advised in the first year. The ABN guidelines then advise that for the other therapies specific alternative monitoring applies. This reference is cited in the footnote on Table 26 of the ERG report. The ERG then use this misunderstanding of theirs as a specific example of the lack of clarity in the costs reported in the Novartis submission.	This sentence on page 86 should read: "The administrative and monitoring costs of fingolimod and Avonex are fully provided by the manufacturer (as highlighted in the above table). The difference in the requirement of tests and visits is based on the respective SPC and the ABN guidelines. "	The sentence on page 86 is inaccurate and misleading	The ERG does not consider there is any factual inaccuracy in the statements made. The ERG sustains its concern over the lack of clarity as to the difference in costs associated with different treatments as it feels there is a lack of discussion as to these differences.

Issue 29 Inconsistent discussion regarding the appropriate time horizon for the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On pages 10, 43, 58, 76, Table 33 (Page 95), and Appendix 1 (Pages 120 and 122) the 50-year time horizon is criticised as being too long. However, in Sections 5, Page 90, and Page 108 of the report the ERG states that a 50-year time horizon is an appropriate length time horizon.	The quotation marks need removing from the statements on pages 10, 43, and 58. The sentence about the time horizons in previous needs removing from pages 10, 43, 58, and 76. Table 33 (Page 95) and Appendix 1 (Pages 120 and 122) need amending to clarify that the justification for the 50-year time horizon in the base case was to meet the specification from NICE that the time horizon is long enough to capture all of the costs and benefits.	The discussion on pages 10, 43, 58, 76, Table 33 (Page 95), and Appendix 1 (Pages 120 and 122) is incorrect and inconsistent with the ERG's view that a 50-year time horizon is appropriate. On pages 60 to 68 the ERG has undertaken an analysis to demonstrate that the 50-year time horizon is correct and a time horizon any shorter will neglect to capture all of the costs and benefits The ERG shows on page 68 that by 34-years only 50% of the patients in the model population are dead. The ERG's analysis on page 60 then shows that after 50 years the vast majority, but not all, of the patients in the model have reached the end of their life. The ERG's analysis also shows that making the time horizon any shorter results in an increase in the proportion of subjects not reaching the end of their life. This analysis by the ERG clearly shows that a time horizon of less than 50 years would be too short.	The ERG does not consider there is any factual inaccuracy in the statements made. The ERG is not criticising the use of a 50 year time horizon in any of the examples presented here. The issue being highlighted is the divergence of structural assumptions used and hence the comparability of model results between the different models.

Issue 30 Inaccurate representation of content of manufacturer submission with regards to the lack of efficacy data for comparator therapies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 22 it states: "Given that over 80% of patients with characteristics approximating those of population 1b were treated with an alternative DMT, the fact that no evidence from head to head comparisons with these alternatives was presented constitutes a clear weakness in the submission which is compounded by the fact that there is mixed evidence as to the relative efficacy of Avonex compared to Rebif and Betaferon"	The sentence should be removed.	This sentence implies that Novartis failed to present data rather than the truth which is that the data is not available. The systematic review carried out by Novartis was unable to identify any studies other than FREEDOMS and TRANSFORMS which reported data for Population1b. The ERG summarised that the systematic review was unlikely to fail to identify studies. This means it is inaccurate to imply this lack of data is the fault of Novartis.	Whilst the ERG do not consider this to be a factual inaccuracy, the ERG did not mean to imply that this was the fault of Novartis and the report has been amended to make this clear. The ERG report now reads (p22): "*Given that over 80% of patients with characteristics approximating those of population 1b were treated with an alternative DMT, the fact that no evidence from head to head comparisons with these alternatives is available constitutes a clear weakness in the evidence base. This is compounded by the fact that there is mixed evidence as to the relative efficacy of Avonex compared to Rebif and Betaferon. While the submission is complete with respect to inclusion of extant head-to-head trials, it is reflective of this limited evidence base."*

Issue 31 The status of the UK marketing authorisation is incorrectly reported

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.2 (Page 21) Here it states: "Fingolimod does not currently have a UK marketing authorisation for use in RRMS. Its anticipated authorisation is for use in adults with RRMS who meet the criteria defined in section 3.1."	It should read: "Fingolimod has UK marketing authorisation for use in adults with RRMS who meet the criteria defined in section 3.1."	Fingolimod received UK marketing authorisation in March 2011 for use in adults with RRMS who meet the criteria defined in section 3.1	The ERG accept this point and the ERG report has been amended (p21) to read: "*Fingolimod has UK marketing authorisation for use in adults with RRMS who meet the criteria defined in section 3.1."*

Issue 32 Unsubstantiated speculation by the ERG about the accuracy of the Novartis submission in regard to figure 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 55 it states: "*No interpretation was provided to explain the shaded area surrounding the majority of the model and some of the lower EDSS states."* The shaded area is to highlight that part of the figure has been enlarged. This is a common feature of technical drawing and is so well understood that explanations are not generally necessary. On page 54 of the PenTAG ERG report for natalizumab a very similar diagram appears. As discussed in the fingolimod	Novartis suggests this sentence is removed.	The statement is unnecessary and has no part in a HTA review. This could have been dealt with in the ERG clarification questions.	The ERG does not consider there is any factual inaccuracy in the statements made. The ERG sustains its concern as to the clarity of the figure. No discussion is made as to if the analysis of this enlarged area is consistent with other EDSS states, or which EDSS the enlarged section applies to.

submission the fingolimod model is heavily based on the model submitted by Biogen for natalizumab. Because the models are structurally so similar it seemed appropriate to be consistent with the diagrams.			

Issue 33 Misunderstanding by the ERG regarding omission of severe infections from the model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 84 and Page 95 mention that "It is unclear why severe infections are excluded from the analysis." In the submission in Table 42 (Page 164) it can be seen that 1.2% of patients receiving fingolimod had severe infections whereas 1.9% of placebo patients had severe infections. The percentage of patients with severe infections in the placebo arm is higher than the fingolimod arm. So Novartis decided it would be counterintuitive to incorporate the infections into the cohort in the model receiving fingolimod.	The sentence on page 84: "Only costs for adverse events ii, iii and iv are considered in the model. Severe infections are excluded from the analysis because the incidence in the trials was higher for placebo."	The omission of infections from the model appeared to be logical to Novartis. This misunderstanding could have been easily discussed in the ERG questions.	The ERG does not consider there is any factual inaccuracy in the statements made. The ERG accepts the reason for the exclusion of severe infections, however, it does not believe that this exclusion was suitably discussed or justified in the submission.

Issue 34 Unsubstantiated additional analysis by the ERG regarding efficacy of Rebiff-44

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In section 6.3 (Page 103) the ERG undertook a series of indirect comparisons in “Population 1b” and “Population 1b minus 2” including the therapy Rebif-44. These are summarised in Table 39 of the ERG report. The only data available for “Population 1b” or “Population 1b minus 2” is from FREEDOMS and TRANSFORMS. FREEDOMS contained the treatment arms Fingolimod and Placebo. TRANSFORMS contains the treatment arms Fingolimod and Interferon beta-1b (Avonex). This means it is not possible to compare to Rebif-44 because there is no data. The ERG then produced a series of cost effectiveness tables based on this analysis - Tables 40, 41, 42, and 43.	The entire section 6.3 needs to be removed.	The data in Tables39, 40, 41, 42, and 43 in the ERG report are not based on any actual real data. So it is unclear how the ERG could arrive at any of these figures. The value of reporting this speculative and unsubstantiated data is unclear.	The ERG does not consider there is any factual inaccuracy in the statements made. The data, methods and results of this analysis are described in section 6.3 of the ERG report.

Issue 35 Inaccurate misrepresentation of manufacturers submission in regard to comparison with previous MS models

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 124 it states: "*Have the results of the model been compared with those of previous models and any differences in results explained?"* The answer given by the ERG on page 124 is: "*N - Models are not compared"*	The answer to the question needs to be changed to: "Yes. The models have been compared"	This is incorrect. On pages 21 and 273 of the Novartis submission there is clear comparison of the results from the fingolimod model to previous MS models.	The ERG does not consider there is any factual inaccuracy in the statements made. This table refers to the economic model not the pharmacodynamic properties of fingolimod as discussed on pages 21 and 273 in the manufacturer's submission.

Issue 36 Typographical error on page 105

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 105 it reads: "The implication being that DMT impact on progression is to some extent double counted in the model" This sentence is concluding a discussion by the ERG about how DMTs have an effect on both progression and relapses, and progression itself has an effect on relapse. Novartis believes the ERG meant to conclude that the DMT impact on relapse is to some extent double counted in the model.	Page 105 should read: "The implication being that DMT impact on relapses is to some extent double counted in the model"	Currently the sentence doesn't logically flow on from the text before it.	The ERG accepts that this is a typo and the report has been amended as suggested.

Issue 37 Typographical error on page 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The sentence reads: "For example the AFFIRM trial had an ARR in the placebo group of 0.78 at 12 months and 0.73 at 24 months (compared to 0.27 and 0.28 respectively for the natalizumab group)." In the referenced cited for this sentence in the ERG report the ARR at 24 months was reported as 0.23	The sentence should read: "For example the AFFIRM trial had an ARR in the placebo group of 0.78 at 12 months and 0.73 at 24 months (compared to 0.27 and 0.23 respectively for the natalizumab group)."	The sentence is incorrect.	The ERG accepts that this is a typo and the report has been amended as suggested.

Issue 38 Two typographical errors on page 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The sentence reads: "The ratio of ARR for population 1b but not for fingolimod 0.5 mg versus Avonex up to month 12 was [redacted] while for fingolimod versus placebo up to month 24 it was [redacted]." The ARR for fingolimod versus placebo was [redacted].	The sentence should read: "The ratio of ARR for population 1b but not 2 for fingolimod 0.5 mg versus Avonex up to month 12 was [redacted] while for fingolimod versus placebo up to month 24 it was [redacted]."	Currently the sentence is incorrect.	The ERG accepts that this is a typo and the report has been amended as suggested.

In addition, there is a 2 missing from the first part of the sentence which describes the subgroup.			The ERG accepts that this is a typo and the report has been amended as suggested.