# National Institute for Health and Care Excellence
# Centre for Health Technology Evaluation

## Pro-forma Response

## ERG report

## Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis

You are asked to check the ERG report from Southampton Health Technology Assessment Centre to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **7 October** 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 proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

### Issue 1 Direct comparison with scoped comparators

| Description of problem | Description of proposed amendment | Justification for amendment |
|---|---|---|
| Page 6, bullet point iv). "The direct comparisons did not include any trials comparing alemtuzumab with the coped [sic] comparators".<br><br>This statement is incorrect, as direct comparison with SC interferon β-1a is, a scoped comparator, is provided in the GMS. Additionally there is a typographical error which should be corrected to state "scoped". | Amend sentence to state:<br><br>"With the exception to SC IFNβ-1a, direct comparisons did not include any trials comparing alemtuzumab with other scoped comparators" | The statement is misleading and implies that only indirect comparison with other comparators has been shown. Alemtuzumab has demonstrated activity in RRMS compared with an active, and NICE scoped, comparator. |

### Issue 2 Subgroup analyses

| | | |
|---|---|---|
| On page 7 it is stated that:<br><br>"Some subgroup analyses on a population with rapidly evolving RRMS were undertaken in two trials. Few results were reported. For SAD at six months the hazard ratio favoured treatment with alemtuzumab in one trial in a treatment naive population. No subgroup analyses were undertaken on those with highly active RRMS who had been previously treated with DMTs."<br><br>It is assumed that this statement relates to the published literature since in the submission both RES and HAD despite interferon use subgroup analysis was presented for ARR, SAD 6 month and 3 month and discontinuation rate outcomes | Suggested alternative wording<br><br>In the published literature, some subgroup analyses on a population with rapidly evolving severe RRMS were undertaken in two trials. Few results were reported. For SAD at six months the hazard ratio favoured treatment with alemtuzumab in one trial in a treatment naive population. No subgroup analyses were reported on those with highly active RRMS who had been previously treated with DMTs. | The statement is misleading because it does not stipulate whether it is referring to analyses within the GMS submission or within the published literature. |

| | | |
|---|---|---|
| in which case reference to this fact should be made. | | |

### Issue 3 Statement on use of natalizumab and fingolimod

| Description of problem | Description of proposed amendment | Justification for amendment |
|---|---|---|
| On page 11 under Section 2.2 the following statement is made:<br>"Currently the preferred treatment for active RRMS is natalizumab and another treatment option is fingolimod."<br>Both natalizumab and fingolimod are limited by their licences and NICE guidance to subgroups of patients who would are considered to have highly active RRMS. Natalizumab is more commonly used than fingolimod in England and wales. | The statement should read:<br>"Currently the preferred treatment for highly active RRMS is natalizumab and another treatment option is fingolimod." | The statement as presently written is inaccurate. The commonest treatments used in active RRMS are the beta interferons and glatiramer acetate |

### Issue 4 Timelines relating to clarification questions

| | | |
|---|---|---|
| Page 11 paragraph 2 states:<br>"Clarification on some aspects of the GMS was requested from the manufacturer by the ERG via NICE on 7th August 2013. A response from the manufacturer via NICE was received by the ERG on 2nd September 2013 and this can be seen in the NICE evaluation report for this Appraisal."<br>The clarification questions were received from NICE by the Manufacturer on 13th | The statement should read:<br>"Clarification on some aspects of the GMS was requested from the manufacturer by the ERG via NICE on 13th August 2013. A response from the manufacturer via NICE was received by the ERG on 2nd September 2013 and this can be seen in the NICE evaluation report for this Appraisal." | Provide accuracy on the timelines regarding the receipt of the clarification questions by the manufacturer. |

| | | |
|---|---|---|
| August and our response was sent back on 29th August | | |

## Issue 5 Marketing authorisation

| Description of problem | Description of proposed amendment | Justification for amendment |
|---|---|---|
| Page 12, Intervention<br>"Currently alemtuzumab does not have marketing authorisation, although a positive CHMP opinion was granted in June 2013 and the indication for treatment is anticipated being for RRMS with active disease defined by clinical or imaging features".<br>Marketing authorisation for alemtuzumab (Lemtrada) was granted by the EMA on 17th September 2013, for the treatment of adult patients who have relapsing-remitting MS with active disease defined by clinical or imaging features. | "Subsequent to the GMS submission, marketing authorisation was granted in September 2013 for the treatment of adult patients who have RRMS with active disease defined by clinical or imaging features. This is consistent with the anticipated population following positive CHMP opinion in June 2013" | The amendment correctly describes the current regulatory status for alemtuzumab and avoids any doubt about the potential licensed population |

## Issue 6 Cost-effectiveness sub-group analysis

| | | |
|---|---|---|
| Page 13, Other relevant factors<br>"The GMS comments that no subgroup analysis in the cost effectiveness analysis was undertaken and that results were pooled from both treatment naive and previously treated populations to capture more appropriately use across the broad range of the license." | "The GMS comments that no subgroup analysis for treatment experienced and treatment naive populations were undertaken in the cost effectiveness analysis. Results were pooled from both treatment naive and previously treated populations to capture more appropriately use across the broad range of the licence. Subgroup analyses were presented in the cost effectiveness analyses in the GMS for "Highly active despite interferon" and "Rapidly Evolving Severe" populations. | The statement is misleading and does not accurately reflect how the GMS addresses the subgroups described in the decision problem |

| | | |
|---|---|---|
| This statement is incorrect in that sub-group analysis for the cost-effectiveness analyses were presented for the “Highly active despite interferons” and “Rapidly Evolving Severe” populations | | |

### Issue 7 Databases searched for the clinical search strategy (1)

| Description of problem | Description of proposed amendment | Justification for amendment |
|---|---|---|
| Page 13, Description of manufacturers search strategy<br>“The GMS used Pubmed in the clinical search strategy and Medline in all other searches”<br>This statement is not clearly explained. | “The GMS accessed Medline and Medline-R through Pubmed for the clinical searches and via Embase for all other searches” | The statement is misleading and implies that the search strategies were completed in different literature databases, where in fact the same literature database was accessed through different portals. Whilst we acknowledge that this is inconsistent it is no less acceptable as accessing Medline via Ovid. |

### Issue 8 Databases searched for the clinical search strategy (2)

| | | |
|---|---|---|
| Page 13, Description of manufacturers search strategy<br>“In addition, Embase is not cited for the clinical searches but is reported for all other searches”<br>This is incorrect. As stated on page 64, 134, 410 and 412 of the GMS, the clinical search strategies were run in Medline and Medline-R (via Pubmed), Embase and CENTRAL | Delete this statement. | The statement is incorrect and does not accurately represent the extent to which searches were completed to identify evidence to inform the estimation of clinical effectiveness and MTC inputs. |

## Issue 9 Description of CAMMS 223 baseline characteristics

| Description of problem | Description of proposed amendment | Justification for amendment |
|---|---|---|
| On page 15 it is stated that **"**The ERG note that in Table B6.3.4 (GMS page 87-9) of the GMS the CAMMS223 trial had approximately 10% of participants with one or zero relapse in the past two years when the inclusion criteria states this should be at least two.<br><br>More precision would help provide a better understanding of the impact of this issue: | Suggested amendment:<br><br>"The ERG note that in Table B6.3.4 (GMS page 87-9) of the GMS the CAMMS223 trial had 7% and 5% of participants with one relapse in the past two years in the placebo and alemtuzumab arms respectively (with an additional 2% of patients in the alemtuzumab arm with zero relapses) when the inclusion criteria states this should be at least two." | More precision would help provide a better understanding of the potential impact of the issue described. |

## Issue 10 Factual error in description of dosing for alemtuzumab and failure to make mention of the extension study part of CARE MS I and II studies which have reported results

| | | |
|---|---|---|
| On Page 17 it is stated that<br><br>"2) CARE MS-I (Cohen and colleagues 20122) is an RCT comparing SC IFNβ-1a (44µg) with IV alemtuzumab 12 mg/day.; 3) CARE MS-II (Coles and colleagues 20123) is an RCT comparing IFNβ-1a (44µg) with IV alemtuzumab 12 mg/day and IV alemtuzumab 24mg/day."<br><br>More precision should be provided on the dosing regime of alemtuzumab since the present wording is misleading<br><br>Mention should be made of the year 3 extension study reported data from CARE MS I and II which provided retreatment rate | Suggested amendment:<br><br>"2)CARE MS-I (Cohen and colleagues 20122) is an RCT comparing SC IFNβ-1a (44µg) with IV alemtuzumab 12 mg/day via intravenous (IV) infusions on 5 consecutive days at baseline and on 3 consecutive days 12 months later;<br><br>3) CARE MS-II (Coles and colleagues 20123) is an RCT comparing IFNβ-1a (44µg) with IV alemtuzumab 12 mg/day and 24mg/day via intravenous (IV) infusions on 5 consecutive days at baseline and on 3 consecutive days 12 months later.<br><br>**Both CARE MS I and II Studies have reported 3 year extension study results which include efficacy and retreatment rate data "** | More precision should be provided on the dosing regime of alemtuzumab since the present wording is misleading. |

| | | |
|---|---|---|
| data (18%-20%) and efficacy data | | |

### Issue 11 Typographical error (1)

| Description of problem | Description of proposed amendment | Justification for amendment |
|---|---|---|
| Page 28, last paragraph<br>There is a missing page cross reference which is noted as XX | Add page number to cross reference and remove green highlighting | Typographical error |

### Issue 12 Unnecessary CIC marking

| | | |
|---|---|---|
| Page 33 / 34, Table 5 – unnecessary CIC marking | It is not necessary to mark as CIC in Table 5 the base case MTC results **with the exception of the alemtuzumab result.**<br>The all years / "all trials" MTC results do need to be marked as CIC as they presently are in the ERG report. | Unnecessary CIC marking |

### Issue 13 Precision in description of MTC result

| | | |
|---|---|---|
| On page 38 it is stated that "Results from the three alemtuzumab trials compared with the other relevant comparators via the MTC can be seen in Table 11. This shows that the comparison between alemtuzumab and [redacted] was statistically significantly different. [redacted]."<br>More precision on what the outcome statement relates to would be helpful. | Suggested amendment:<br>"Results from the three alemtuzumab trials compared with the other relevant comparators via the MTC for 6 months SAD can be seen in Table 11. This shows that the comparison between alemtuzumab and [redacted] was statistically significantly different. [redacted]." | More precision on what the outcome statement relates to would be |

| | | |
|---|---|---|
| | | helpful |

## Issue 14 Correct description of reported outcome

| Description of problem | Description of proposed amendment | Justification for amendment |
|---|---|---|
| On page 44 paragraph 3 it is stated that:<br>“The GMS reported that in the CAMMS223 trial, the estimated proportion of participants in the two alemtuzumab subgroups with SAD at six months was 91% (95% CI 84.0, 95.2) compared with 73% (95% CI 58.1, 83.5) in the IFNβ-1a subgroup, HR 0.30 (95% CI 0.13, 0.69), p=0.0045”.<br>These percentages refer to SAD free patients not those with SAD. | The statement should read:<br>“The GMS reported that in the CAMMS223 trial, the estimated proportion of participants in the two alemtuzumab subgroups who were SAD free at six months was 91% (95% CI 84.0, 95.2) compared with 73% (95% CI 58.1, 83.5) in the IFNβ-1a subgroup, HR 0.30 (95% CI 0.13, 0.69), p=0.0045”. | Ensure correct description of the outcome reported |

## Issue 15 Typographical error (2)

| | | |
|---|---|---|
| Page 43 and 44.<br>Reference to the authors name is incorrectly cited as Confayreux (2012) when it should be correctly cited as Confavreux | Correct spelling to state “Confavreux” throughout | Typographical error |

## Issue 16 Marking of confidential information (1)

| | | |
|---|---|---|
| Page 46, line 1 “pyrexia”…. is not marked CIC as per the GMS. | ...“and headache [redacted], rash [redacted], pyrexia [redacted], and MS relapse [redacted]” | Confidential information. |

## Issue 17 Marking of confidential information (2)

| Description of problem | Description of proposed amendment | Justification for amendment |
|---|---|---|
| Page 47, paragraph 3.<br>Anaphylactic reactions data has not been marked CIC due to a mistake in the GMS. | "Anaphylactic reactions: (defined according to the Sampson Standardised MedDRA Queries (SMQ) criteria) were identified in [redacted] of patients in the alemtuzumab 12 mg group (treatment cycle 1: [redacted]%, cycle 2: [redacted]%, cycle 3: [redacted]%, cycle 4 and 5: 0%)." | Confidential information. Mistake of CIC marking in GMS – will correct when resubmit CIC marking on 11/10/13 |

## Issue 18 Marking of confidential information (3)

| | | |
|---|---|---|
| Page 50, paragraph 2, line 6.<br>"SAEs were reported in……" should be marked CIC. | "SAEs were reported in [redacted] of the IFNβ-1a and [redacted] of the 12mg alemtuzumab treated patients at year 3 in the CAMMS223 trial" | Marked as confidential information in Appendix 9 of GMS (detailed safety for CAMM223 comes from the CSR, rather than Coles 2008 which is why it is CIC). |

## Issue 19 Typographical error (3)

| | | |
|---|---|---|
| Page 54.<br>"The ERG considers it unlikely that any cost-effectiveness studies of **rivaroxaban** were missed by the manufacturer as the literature search methods appear sound." | Correct to state "The ERG considers it unlikely that any cost-effectiveness studies of alemtuzumab were missed by the manufacturer as the literature search methods appear sound." | Typographical error |

## Issue 20 Relapse severity data

| | | |
|---|---|---|
| Page 62.<br>"Relapse severity is also included in the model and data sourced from the systematic review of natural history **although no details are given of the** | Delete the second half of the statement "Relapse severity is also included in the model and data sourced from the systematic review of natural history" | The statement is incorrect and implies a question about the robustness of the approach taken in the cost-effectiveness modelling. |

| | | |
|---|---|---|
| **methods used**”<br>This statement is incorrect in that the methods for the natural history systematic review and how the data was applied to the model is described in Appendix 10 and Section 7. | | |

## Issue 21 Typographical error (4)

| Description of problem | Description of proposed amendment | Justification for amendment |
|---|---|---|
| Page 65.<br>“This provided an index of disutilities of 0.00 at EDSS to 0.14 at EDSS 8.5 – 9.5” | Correct to state “This provided an index of disutilities of 0.00 at EDSS 0 to 0.14 at EDSS 8.5 – 9.5” | Typographical error |

## Issue 22 Treatment effect

| | | |
|---|---|---|
| Page 79.<br>“The GMS model assumes that the treatment effect continues at the same rate long term.”<br>This statement applies to the base case. As stated on page 274 of the GMS, “to test the sensitivity of the model to waning treatment effect, scenario analyses have been performed based on results of the systematic review for long term efficacy.” | Correct to state “The GMS model assumes that the treatment effect continues at the same rate long term in the base case.” | Clarification of assumptions made by manufacturer. |