**Evidence Review Group - SHTAC**

**Alemtuzumab for relapsing-remitting multiple sclerosis**

**Erratum to ERG report**

## Amended paragraphs

Page 6, bullet point iv

a mixed treatment comparison (MTC) based on the literature review for the head-to-head trials. *With the exception to SC IFNβ-1a*, direct comparisons did not include any trials comparing alemtuzumab with other scoped comparators.

Page 7, paragraph 4

*Some subgroup analyses on a population with rapidly evolving RRMS were undertaken in two trials. Few results were reported and not all were tested statistically.*

Page 11, Section 2.2

Currently the preferred treatment for *highly* active RRMS is natalizumab and another treatment option is fingolimod.

Page 12

*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.*

Page 13, Other relevant factors

*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*

Page 13, Description of manufacturers search strategy

*The GMS accessed Medline and Medline-R through Pubmed for the clinical searches and via Embase for all other searches*

Page 13, Description of manufacturers search strategy

Statement '*In addition, Embase is not cited for the clinical searches but is reported for all other searches'* to be deleted

Page 15

The ERG clinical advisors state that the populations in the trials are reasonably typical of those likely to receive DMTs in the UK. The ERG note that in Table B6.3.4 (GMS page 87-9) of the GMS the CAMMS223[1] 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 *(see Table 1 for precise details).*

Page 17 bullet point 2 and 3

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;*

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*.

Page 28

The combined results are reported as relative risks (RR), *see ERG report page 36-40*. The GMS presented RR and 95% confidence intervals (CI) stating that the results were statistically significant (in that the CIs do not include 1)
[redacted] No forest plots were presented for the direct meta-analysis, the GMS refers to the network meta-analysis (section 6.7) for any forest plots.

Page 33/34

**Table 1 Comparison of three month SAD hazard ratios from base case and all trial MTC versus direct evidence**

| | Base case MTC | All trials MTC | Direct |
|---|---|---|---|
| Alemtuzumab 12 mg | [redacted] | [redacted] | None |
| IFNβ-1b 250 µg | 1.21 (0.68 – 2.16) | [redacted] | 0.68 (0.4 – 1.17) |
| Intramuscular (IM) IFNβ-1a | 0.91 (0.61 – 1.33) | [redacted] | None |
| SC IFNβ-1a | 0.79 (0.51 – 1.24) | [redacted] | 0.65 (0.45 – 0.94) |
| GA 20 mg | 0.93 (0.59 – 1.45) | [redacted] | 0.93 (0.65 – 1.32) |
| Fingolimod 0.5 mg | 0.75 (0.58 – 0.96) | [redacted] | 0.76 (0.61 – 0.94) |
| Natalizumab 300 mg | 0.58 (0.4 – 0.84) | [redacted] | 0.58 (0.28 – 1.19) |
| Note: in addition the trials of SC IFNβ1-a versus placebo and of IFNβ1-b versus placebo that were excluded for being recruiting patients prior to 2000, two trials reporting relevant data for GA 20 mg versus placebo were also excluded from the base case MTC | | | |

Page 44 paragraph 3

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.

Page 46

The incidence of AEs for all alemtuzumab 12 mg-treated patients (pooled data) over all available follow-up was [redacted](cumulative up to and including 31/12/2011). Overall incidence of AEs for patients treated with alemtuzumab declined [redacted]. Subgroup data per the number of treatment courses given were not presented, which may have been more representative of incidence rates and explain the decline. The GMS (page 191) cites skin and subcutaneous tissue disorders [redacted]), nervous system disorders [redacted] and infections and infestations [redacted] as the three most frequently affected MedDRA system organ classes, and [redacted], [redacted] and MS relapse [redacted] as the most common AEs (pooled data). The incidence of thyroid AEs increased from [redacted] in year 1 to [redacted] (GMS page 192). The GMS suggests that this is due to higher incidences of [redacted] Table 17 presents grouped AEs reported at a ≥5% incidence in alemtuzumab-treated patients (pooled data) as this was relevant to the economic evaluation.

Page 47

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%)

Page 50

SAEs were reported in [redacted] of the IFNβ-1a and [redacted] of the 12mg alemtuzumab treated patients at year 3 in the CAMMS223 trial.

Page 54

The ERG considers it unlikely that any cost-effectiveness studies of *alemtuzumab* were missed by the manufacturer as the literature search methods appear sound.

Page 62

*Relapse severity leading to hospitalisation*
Relapse severity is also included in the model and data sourced from the systematic literature review of natural history *[although no details are given of the methods used]* to be deleted.

Page 65

This provided an index of disutilities of 0.00 at EDSS *0 to* 0.14 at EDSS 8.5 – 9.5

Page 79

The GMS model assumes that the treatment effect continues at the same rate long term *in the base case.*