# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Premeeting briefing

## Alemtuzumab for treating relapsing-remitting multiple sclerosis

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

## Key issues for consideration

- Are the patients enrolled in the alemtuzumab trials (CARE-MS I, CARE-MS II, CAMMS223 and extension study) similar to UK patients with relapsing-remitting multiple sclerosis (RRMS) who would be treated with alemtuzumab?
- Where in the treatment pathway should alemtuzumab be considered?
  - Is it appropriate to consider alemtuzumab:
    - ◊ as an alternative to interferons and glatiramer acetate, but not best supportive care?
    - ◊ as an alternative to natalizumab for rapidly evolving severe RRMS (RES) and to fingolimod for highly active RRMS?
    - ◊ as an additional treatment in the pathway before or after another disease modifying treatment?
- How do clinicians decide when to start and stop alemtuzumab? Would most patients require only 2 cycles of treatment, or on-going annual treatment? ([redacted] of patients in the trial had a third cycle of treatment)?

### *Clinical effectiveness*

- Which of the manufacturer's mixed treatment comparisons (MTCs) is the most appropriate for estimating the relative clinical effectiveness of the treatments – the base case analysis, which excluded studies that recruited patients before 2000, or the 'All Years from 1980' analysis?
- Is it appropriate for the manufacturer to focus on the outcome of sustained accumulation of disability (SAD) lasting for at least 3 months, rather than lasting at least 6 months?
- Are the 3 studies with alemtuzumab (CAMMS223, CARE-MS I and CARE-MS II) and the trials without alemtuzumab included in the manufacturer's mixed treatment comparison sufficiently long to capture the outcomes of interest in RRMS including relapse rates and disability progression?
- Is it reasonable to assume that a patient would receive best supportive care for the remainder of their life following treatment with alemtuzumab?

### *Cost effectiveness*

- The base case analysis uses the London Ontario dataset (collected in 1989) for the natural history of the disease (for the probabilities of patients with RRMS moving between EDSS health states). Previous NICE appraisals have questioned the use of this dataset because it does not include data from patients whose condition improved (i.e. moved to a lower EDSS state). Should the model be adjusted for transitioning to an improved EDSS state?
- Is it reasonable to assume 100% efficacy for alemtuzumab throughout the model lifetime – that is, the effect of alemtuzumab does not wane over time even in years when a patient has not received a dose?
- Is it reasonable to assume that all comparator treatments have no sustained treatment effect and that once treatment stops, the patient will switch to best supportive care?

# 1 Background: clinical need and practice

1.1 Multiple sclerosis is a chronic, autoimmune disease of the central nervous system that damages myelin and results in inflammation and tissue

damage. This impairs transmission of electrical impulses between the brain, spinal cord and other parts of the body, and leads in most patients to progressive neurological impairment and severe disability. Symptoms can include pain, poor muscle tone including weakness or spasticity, chronic fatigue, unsteady gait, speech problems, incontinence, vision problems and cognitive impairment. The causes of multiple sclerosis are unknown, but genetic and environmental factors play a role. Smoking is a risk factor for multiple sclerosis, as is distance from the equator, suggesting a role for ultraviolet radiation or vitamin D.

1.2 Approximately 100,000 people in the UK have multiple sclerosis, and about 2500 people are newly diagnosed each year. Most people diagnosed with multiple sclerosis are between 20 and 40 years old, and the condition is approximately three times more common in women than in men. Multiple sclerosis has an unpredictable course with variable severity and speed of progression.

1.3 Different types of disease pattern are recognised including relapsing-remitting MS and primary-progressive MS. Relapsing-remitting MS (RRMS) occurs when the person experiences an average of one or two relapses per year, with good or complete remission in between. Primary-progressive MS is when people experience gradual disability over time without remission. Some people with relapsing-remitting MS will develop secondary-progressive MS (SPMS) which is characterised by worsening disability over time rather than relapses followed by recovery.

1.4 RRMS affects approximately 85% of people at time of diagnosis, and is characterised by periods of remission followed by relapses. A subform of RRMS labelled ‘highly active’ characterises more severe disease defined by the number and severity of relapses and by persistent disability caused by the relapses. Highly active RRMS can include:

- ‘Rapidly-evolving’ severe relapsing-remitting multiple sclerosis defined:

    - by 2 or more disabling relapses in 1 year, **and**
    - 1 or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI.
- Adults with high disease activity despite treatment with a beta interferon (normally at least one year of treatment). Patients have:
    - had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 gadolinium-enhancing lesion, **or**
    - an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

1.5 The life expectancy of patients in the UK with multiple sclerosis is between 5 and 10 years shorter than of the general population and there is no cure. Neurologists offer patients treatments to decrease the frequency and severity of relapses, reduce size and number of lesions observed on brain and spinal MRIs, slow physical disability, and maintain or improve patients' quality of life. Current pharmacological management of RRMS includes the first-line use of disease-modifying therapies to reduce the frequency and severity of relapses. These include beta interferon and glatiramer acetate. Neither, however, are currently recommended by NICE (technology appraisal guidance 32; see Appendix A), but are available in the NHS through a risk-sharing scheme (based on an agreement between the Department of Health and the manufacturers). Neurologists may offer beta interferon or glatiramer acetate if the patient meets the criteria described in the Association for British Neurologist (ABN) Guidelines that is, adults who can walk (maximum Expanded Disability Status Scale [EDSS] score of 6.5; higher numbers reflect great disability) with active relapsing disease defined as 2 clinically significant relapses in the previous 2 years. The scheme provides drugs at a price which DH considers cost effective. The patients prescribed drugs in the

scheme are monitored annually and the cost of medicines are adjusted if the outcomes differ from the target agreed between the DOH and the manufacturers.

1.6 In practice, for people whose disease has responded inadequately to first-line treatment, clinicians may offer as second line treatment a different beta interferon or glatiramer acetate, or escalate the dose of the existing beta interferon. Some people experience problems with beta interferon and glatiramer acetate because they must inject them or because they sometimes cause flu-like symptoms, fatigue, and depression. For people with rapidly-evolving severe RRMS, natalizumab is recommended as an option (NICE technology appraisal guidance 127; see Appendix A). For adults with highly active RRMS who have an unchanging relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon, NICE has recommended fingolimod (with a patient access scheme) as an option (NICE technology appraisal guidance 254; see Appendix A). There is no fixed treatment pathway for multiple sclerosis, and neurologists choose treatments based on efficacy and safety, as well as on patient preference.

# 2 The technology

2.1 Alemtuzumab (Lemtrada, Genzyme) is a monoclonal antibody which binds to the CD52 antigen on B and T lymphocytes and monocytes, initiating cell lysis and reducing their circulating numbers. The mechanism of action for alemtuzumab on RRMS is not fully understood. Alemtuzumab received a UK marketing authorisation for treating adults with RRMS with active disease defined by clinical or imaging features in September 2013. The recommended dose of alemtuzumab is 12 mg/day administered by intravenous infusion for 2 treatment courses with an initial treatment course of 5 consecutive days followed by the second treatment of 3 consecutive days administered 12 months later. Alemtuzumab also had a UK marketing authorisation for treating B-cell chronic lymphocytic leukaemia, but was withdrawn from use in August, 2012.

2.2 The draft summary of product characteristics lists the following adverse reactions for alemtuzumab: autoimmunity (idiopathic thrombocytopaenic purpura, thyroid disorders, nephropathies, cytopaenias), infusion-associated reactions, rash, headache, pyrexia, and respiratory tract infections. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The indicative price of alemtuzumab (to be confirmed following agreement with the Department of Health; excluding VAT) is £7,045 per vial which equates to £56,360 for the full course of treatment consisting of 5 consecutive 12mg doses in year 1, followed by 3 consecutive 12 mg doses in year 2.

# 3 Remit and decision problem

3.1 The remit from the Department of Health for this appraisal is: to appraise the clinical and cost effectiveness of alemtuzumab within its licensed indication for treating relapsing-remitting multiple sclerosis.

| | **Final scope issued by NICE** | **Manufacturer's decision problem** | **Evidence Review Group (ERG) comments** |
|---|---|---|---|
| Population | People with relapsing-remitting multiple sclerosis | People with active relapsing-remitting multiple sclerosis based on clinical or imaging features | Appropriate |
| Comparators | • Beta-interferon<br>• Glatiramer acetate<br>• Natalizumab (for treatment-naïve or previously treated patients with **rapidly-evolving severe** RMSS)<br>• Fingolimod (for patients with highly **active** RMSS who have received treatment with beta interferon) | 1. Beta-interferon<br>2. Glatiramer acetate<br>3. Natalizumab (for treatment-naïve or **previously treated patients with rapidly-evolving severe** RMSS)<br>4. Fingolimod (for patients with **highly active** RMSS who have received treatment with beta interferon)<br>5. In addition | Comparators in the submission reflect those in the scope. In addition, the submission includes comparisons with fingolimod and natalizumab for populations which are broader than their respective licenses, i.e. in the **active** RRMS |

| | | | |
|---|---|---|---|
| | | natalizumab and fingolimod included as comparators for active RRMS | populations. |
| Outcomes | • Relapse rate<br>• Severity of relapse<br>• Disability (for example, expanded disability status scale [EDSS])<br>• Symptoms of multiple sclerosis (such as fatigue, cognition and visual disturbance)<br>• Freedom from disease activity<br>• Mortality<br>• Adverse effects of treatment<br>• Health-related quality of life | As per scope and in addition:<br>• Hospitalisation (as a result of relapses). | Outcomes appear appropriate |
| Subgroups | If the evidence allows, the following subgroups of patients will be considered:<br>• Treatment experienced patients with RMSS<br>• Treatment naïve patients with RMSS<br>• Patients with highly active relapsing-remitting multiple sclerosis whose disease has inadequately responded to or are intolerant to treatment with disease modifying therapy<br>• Patients with rapidly evolving severe RMSS | • Patients with highly active RMSS despite an adequate course of interferon (in line with the fingolimod licence)<br>• Patients with rapidly evolving severe RMSS (in line with the natalizumab licence) | Data were available to assess treatment naive and previously treated populations in subgroups as per the NICE scope; however, the manufacturer did not undertake the analyses |

# 4 Clinical-effectiveness evidence

4.1 The manufacturer provided clinical-effectiveness evidence, identified through systematic review from:

- 2 phase III randomised controlled clinical trials: CARE-MS I (n=581, median follow up of 24 months), and CARE-MS II (n=1046, median follow up of 24 months)

- 1 phase II trial: CAMMS223 (n=334, 36 months maximum follow up, extended to 48 months maximum follow up
- 1 extension study: CAMMS03409 (n= 1322, median 7.1 years follow-up) which enrolled people with RRMS from the CARE-MS I, CARE-MS II and CAMMS223 studies (all participants received alemtuzumab as needed, regardless of prior treatment).

In addition, the manufacturer submitted 2 mixed treatment comparisons: one to compare alemtuzumab to interferon beta-1a, and another to compare alemtuzumab to other treatments for RMSS.

4.2 CARE-MS I, CARE-MS II and CAMMS223 compared the effectiveness of alemtuzumab (12 mg per infusion or 24 mg per infusion [in CARE-MS II only]) with subcutaneous interferon beta-1a (44 µg, 3 times weekly after dose titration). Each of the phase III multicentre trials included sites in the UK. The manufacturer also provided a meta-analysis that included all 3 trials to estimate the effectiveness of alemtuzumab (12 mg) vs. interferon beta-1a (44 µg). All people participating in CARE-MS II had received disease-modifying therapies previously, whereas people in the CARE-MS I and CAMMS223 studies were naïve to treatment. People in the CARE-MS II trial had a greater time between their first relapse and study enrolment than people in CARE-MS I [redacted]. An extension study to CARE-MS I and CARE-MS II trials to assess the long-term efficacy and safety of alemtuzumab opened in January 2010 and is due to report in February 2016.

4.3 The primary outcomes of the 3 trials were time to the onset of sustained accumulation of disability (SAD) (that lasted for 6 months in the CARE-MS I and CARE-MS II trials), and relapse rate (‘co-primary outcomes’). In both CARE-MS trials patients were assessed every quarter using the EDSS, and were assessed as needed for suspected relapses. SAD was defined as an increase of at least 1.5 points for patients with a baseline score of 0 and of at least 1.0 point for patients with a baseline score of 1.0 or more. A relapse was defined as new or worsening neurological symptoms

attributable to MS, lasting at least 48 hours, without pyrexia, after at least 30 days of clinical stability, with an objective change on neurological examination. All 3 trials had intention-to-treat analyses; although in CARE-MS I and CARE-MS II the population analysed included only those patients who had received at least one dose of study medication which suggests a modified intention-to-treat (ITT) analysis. In CAMMS223 the ITT analyses were unadjusted but in the CARE-MS I and CARE-MS II analyses were adjusted for geographical region.

4.4 The secondary outcomes presented by the manufacturer included the proportion of relapse-free patients, change in EDSS, percentage change in T2-hyperintense lesion volume and change in multiple sclerosis functional composite.

4.5 The manufacturer's meta-analysis of the 3 trials included 6 outcomes:

- annualised relapse rate,
- proportion of patients relapse-free,
- SAD that lasted for 3 months,
- SAD that lasted for 6 months,
- discontinuation of study drug for any reason and
- discontinuation of study drug because of adverse events.

4.6 The baseline characteristics of the trial participants are summarised in Table 1. The inclusion criteria of the 3 trials specified the number of previous relapses a patient must have to enrol in each study. For CARE-MS I and CARE-MS II this was at least 2 relapses within the previous 2 years, with at least 1 within the previous year. For CAMMS223 this was at least 2 relapses in the previous 2 years. CARE-MS I and CAMMS223 included people with an EDSS score between 0 and 3 (where 0 means no disability and no signs of impairment in any functional system and 3 means moderate disability in 1 functional system, or mild disability in 3 or 4 functional systems, but with unimpaired walking), whereas CARE-MS II included people with an EDSS score between 0 and 5 (where 5 means

disability severe enough to impair full daily activities and ability to work a full day without special provisions, but where a person is still able to walk for 200m without aid or rest).

**Table 1 Trial baseline characteristics**

| | **CAMMS223** | | **CARE-MS I** | | **CARE-MS II** | |
|---|---|---|---|---|---|---|
| | SC IFNβ-1a (44µg) | Alemtuzumab (12mg)[a] | SC IFNβ-1a (44µg) | Alemtuzumab (12mg) | SC IFNβ-1a (44µg) | Alemtuzumab (12mg)[a] |
| **Number** | 111 | 112 | 187 | 376 | 202 | 426 |
| **Mean age (SD) years** | 32.8 (8.8) | 31.9 (8.0) | 33.2 (8.5) | 33.0 (8.0) | 35.8 (8.8) | 34.8 (8.4) |
| **Female (%)** | 64.0 | 64.3 | 65.2 | 64.6 | 64.9 | 66.0 |
| **White (%)** | 90.1 | 91.1 | 96.3 | 93.6 | 92.6 | 90.4 |
| Relapse in previous 2 years (%): | | | | | | |
| 0 | 0 | 2 (1.8) | [redacted] | [redacted] | [redacted] | [redacted] |
| 1 | 8 (7.2) | 6 (5.4) | [redacted] | [redacted] | [redacted] | [redacted] |
| 2 | 73 (65.8) | 58 (51.8) | [redacted] | [redacted] | [redacted] | [redacted] |
| ≥3 | 30 (27.0) | 46 (41.1) | [redacted] | [redacted] | [redacted] | [redacted] |
| **Mean (SD) relapses** | - | - | [redacted] | [redacted] | [redacted] | [redacted] |
| **Mean duration of previous MS drug use in months (SD)** | - | - | - | - | 36 (23.7) | 35 (25.0) |
| **Mean EDSS score** | 1.9 (0.83) | 1.9 (0.74) | [redacted] | [redacted] | [redacted] | [redacted] |
| 0 | 8 (7.2) | 4 (3.6) | [redacted] | [redacted] | [redacted] | [redacted] |
| >0-1.5 | 37 (33.3) | 40 (35.7) | [redacted] | [redacted] | [redacted] | [redacted] |
| >1.5-2.0 | 28 (25.2) | 30 (26.8) | [redacted] | [redacted] | [redacted] | [redacted] |
| >2.0-3.0[b] | | 38 (33.9) | 65 (35) | 140 (37) | 48 (24) | 112 (26) |
| >3.0-4.0[b] | - | 0 | 3 (2) | 8 (2) | 50 (25) | 98 (23) |
| >4.0-5.0[b] | - | - | - | - | 19 (9) | 42 (10) |
| >5.0-6.0[b] | - | - | - | - | 2(1) | [redacted] |
| >6.0-7.0[b] | - | - | - | - | 0 | [redacted] |

SC IFNβ-1a – subcutaneous interferon beta-1a
[a] Also had a third treatment arm with alemtuzumab 24 mg not reported here as not the anticipated licensed dose

### Alemtuzumab compared with subcutaneous interferon beta-1a

4.7 In CARE-MS I, the rates of SAD lasting for 6 months did not significantly differ between the alemtuzumab and subcutaneous interferon beta-1a arms of the trial. In CARE-MS II, 13% of people in the alemtuzumab arm had SAD lasting for 6 months compared with 20% of people in the subcutaneous interferon beta-1a arm, corresponding to a 42% improvement with alemtuzumab (HR 0.58, 95% CI 0.38–0.87; p=0·008). In

the CAMMS223 study, alemtuzumab compared with subcutaneous interferon beta-1a significantly reduced the risk of SAD lasting for at least 6 months by 75% (HR 0.25; 95% CI: 0.11, 0.57; p<0.001) and the proportion of patients experiencing SAD lasting for at least 6 months at 3 years was 8.5% with alemtuzumab and 26.2% with subcutaneous interferon beta -1a. Alemtuzumab also reduced the rate of relapse by 69% compared with subcutaneous interferon beta-1a. The hazard ratios (HR) of a relapse were 0.45 (95% CI 0.32–0.63; p<0.0001), 0.51 (95% CI 0.39–0.65; p<0·0001) and 0.31(95% CI 0.18-0.52; p<0.001) in the CARE-MS I, CARE-MS II and CAMS223 studies respectively.

4.8 The extended follow-up study of CAMMS223 showed that at 5 years alemtuzumab reduced the risk of SAD lasting for at least 6 months by 69% as compared with subcutaneous interferon beta-1a (HR 0.31 [95% CI 0.16-0.60]; p = 0.0005). The study also showed that over 5 years, alemtuzumab lowered the rate of relapse by 66% compared with subcutaneous interferon beta-1a (HR 0.34 [95% CI 0.20-0.57); p < 0.0001).

4.9 The manufacturer presented the results of the meta-analysis which showed that alemtuzumab was consistently more effective than subcutaneous interferon beta-1a 44 µg for the analysed efficacy and safety outcomes. The result of the meta-analysis for comparison with the direct trial evidence is presented in Table 2.

**HA and RES subgroup analysis**

4.10 The trial populations with highly active (HA) RRMS and rapidly evolving severe (RES) RRMS were used for subgroup analyses. The manufacturer's subgroup analysis combined the HA RRMS and RES RRMS subgroups having considered that the definitions for each group were sufficiently similar. The manufacturer's analysis showed that the effectiveness of alemtuzumab in this subgroup was comparable to or greater than that seen in the overall study populations. In this subgroup of the CAMMS223 and CARE-MS II study populations, people receiving

alemtuzumab compared with subcutaneous interferon beta-1a showed lower relapse rates (81% reduction [p<0.0001] for CAMMS 223 and a 56% reduction [p=0.0018] for CARE-MS II), less sustained accumulation of disability (65% lower risk of SAD lasting at least 6 months [p=0.036] in CAMMS223 and 51% reduction [no p value reported] in CARE-MS II) and a more favourable mean change from baseline EDSS (net mean EDSS improvement by 0.98 point [95% CI: 0.58, 1.39, p<0.0001] in CAMMS223, and 0.24 point improvement [no CI reported] in CARE-MS II).

**Table 2 Clinical trial and meta-analysis results (alemtuzumab compared to subcutaneous interferon beta-1a)**

| Outcome measure | Trials | Relative Risk (95% CI) |
|---|---|---|
| Annual relapse rate | CAMMS223 | 0.31 [0.21, 0.45] |
| | CARE-MS I | 0.46 [0.36, 0.58] |
| | CARE-MS II | 0.5 [0.41, 0.61] |
| | Direct Meta-Analysis | [redacted] |
| Proportion relapse free | CAMMS223 | 2.5 [1.39, 4.51] |
| | CARE-MS I | 2.43 [1.67, 3.55] |
| | CARE-MS II | 2.18 [1.55, 3.07] |
| | Direct Meta-Analysis | [redacted] |
| SAD lasting 3-months | CAMMS223 | [redacted] |
| | CARE-MS I | [redacted] |
| | CARE-MS II | [redacted] |
| | Direct Meta-Analysis | [redacted] |
| SAD lasting 6 months | CAMMS223 | 0.25 [0.11, 0.57] |
| | CARE-MS I | 0.7 [0.39, 1.24] |
| | CARE-MS II | 0.58 [0.38, 0.89] |
| | Direct Meta-Analysis | [redacted] |
| All cause discontinuation | CAMMS223 | 0.24 [0.12, 0.47] |
| | CARE-MS I | 0.28 [0.14, 0.55] |
| | CARE-MS II | 0.24 [0.14, 0.4] |
| | Direct Meta-Analysis | [redacted] |
| AE-related discontinuation | CAMMS223 | 0.14 [0.03, 0.62] |
| | CARE-MS I | 0.22 [0.07, 0.63] |
| | CARE-MS II | 0.41 [0.1, 0.88] |
| | Direct Meta-Analysis | [redacted] |

### Alemtuzumab compared with all comparators in a mixed treatment comparison

4.11 The manufacturer also presented a mixed treatment comparison (MTC) that compared alemtuzumab with each of the treatments in the decision

problem (subcutaneous interferon beta-1a, intramuscular interferon beta-1a, interferon beta-1b, glatiramer acetate, natalizumab and fingolimod). The manufacturer included in its MTC 30 clinical trials identified in the systematic literature review, which recruited patients from the year 2000 onwards, and included at least 80% of patients with relapsing- remitting MS. The manufacturer provided a separate 'All Years' analysis that included studies recruiting participants from 1980. The manufacturer justified the year 2000 as an appropriate cut-off point before which to exclude trials because annualised relapse rates have fallen in recent years and in diagnostic criteria used in MS trials have changed. After 2000, clinicians have used the McDonald criteria which identify MS earlier than the previously used Poser criteria. The outcomes presented in the MTC included annualised relapse rate, proportion relapse free, SAD lasting for 3 months, SAD lasting for 6 months, discontinuation rate and discontinuation rate due to adverse events. The manufacturer used a Bayesian random effects model. The manufacturer also compared the outputs of the base case MTC and all years sensitivity analysis with direct trial evidence in relation to SAD lasting 3 months. The results from the base case MTC are presented in Table 3 below.

4.12 In UK clinical practice a dose of 22 µg subcutaneous interferon beta-1a can be used to treat RRMS for patients who cannot tolerate the higher dose of 44 µg. However, the manufacturer identified no studies using this dose that recruited patients after 2000 for the MTC and therefore the results presented in Table 3 refer to the 44 µg dose. The 22 µg dose of subcutaneous interferon beta-1a was considered separately; based on the results of a separate MTC that included studies with patient recruitment prior to 2000. The manufacturer estimated that 22 µg subcutaneous interferon beta-1a [redacted] the risk of SAD lasting 3 months compared with placebo [redacted] 95% CI not reported) and that alemtuzumab was associated with [redacted] all-cause discontinuations than subcutaneous interferon beta-1a 22µg ([redacted], 95% CI not reported).

**Table 3 Mixed treatment comparison results (comparators versus alemtuzumab)**

| | Annual relapse rate (rate ratio) (95% CrI) | Proportion relapse-free (odds ratio) | 3-month SAD (hazard ratio) | 6-month SAD (hazard ratio) | Total discont-inuation (odds ratio) | Discontinuation to AEs (odds ratio) |
|---|---|---|---|---|---|---|
| **Base case (post-2000) results, 80% RRMS** | | | | | | |
| Alemtuzumab 12 mg (vs placebo) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Alemtuzumab vs IFNβ-1b 250 µg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Alemtuzumab vs IM IFNβ-1a 30 µg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Alemtuzumab vs SC IFNβ-1a 44 µg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Alemtuzumab vs GA 20 mg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Alemtuzumab vs Fingolimod 0.5 mg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Alemtuzumab vs Natalizumab 300 mg | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

[redacted] not statistically significant; all at 95% credible interval.
IFNβ-1b – interferon beta-1b, IM IFNβ-1a – intramuscular interferon beta-1a, SC IFNβ-1a – subcutaneous interferon beta-1a, GA – glatiramer acetate

## Highly active and rapidly evolving severe disease subgroup analyses

4.13 The manufacturer conducted 2 separate indirect comparisons of alemtuzumab for the subgroups of patients with HA and RES disease in CARE MS II. In the manufacturer's subgroup analyses, alemtuzumab led to a statistically significant relative risk reduction in the annualised relapse rate when compared with subcutaneous interferon beta-1a 44µg or fingolimod in the HA subgroup, but not when compared to intramuscular interferon beta-1a 30µg. Results were similar in the RES subgroup when alemtuzumab was also compared to natalizumab. Treatment with alemtuzumab led to a statistically non-significant improvement in 3-month SAD compared with subcutaneous interferon beta-1a 44µg and fingolimod in the HA subgroup. Results were similar in the RES subgroup when alemtuzumab was also compared to natalizumab.

### Adverse events

4.14 The manufacturer stated that almost all patients treated with alemtuzumab reported at least 1 adverse event. In a pooled analysis of CAMMS223, CARE-MS I, CARE-MS II and CAMMS3409, most patients treated with alemtuzumab [redacted] reported at least 1 adverse event, the majority of which were mild or moderate in severity. The incidence of grade 3, 4, and 5 adverse events over the duration of all the studies were [redacted], [redacted], respectively. The most common adverse events were [redacted].

4.15 The incidence of serious adverse events was [redacted] based on all trials over the available follow up (year 4). The most frequently reported serious AEs for the alemtuzumab group were [redacted]. The rate of serious AEs by number of treatment cycles received was [redacted] across courses in the alemtuzumab-treated group [redacted]. With the exception of thyroid disorders, administering more than 2 treatment cycles of alemtuzumab did not result in increased frequencies of common AEs or clinically important events which had not already been observed after 1 or 2 treatment cycles. Over the available follow-up, [redacted] of patients treated with alemtuzumab discontinued treatment because of a serious adverse event.

4.16 [redacted].

4.17 Thyroid disease was observed in an estimated 36.2% of patients during the 4 years after the first course of treatment. The risk of experiencing a first thyroid adverse event was increased between years 2 and 4, with the highest rates seen between years 2 and 3. Serious thyroid events occurred in [redacted] of all alemtuzumab-treated patients over all available

follow-up. Most thyroid disease was managed with conventional medical therapy and less than [redacted] required surgical treatment.

4.18 A total of [redacted] people treated with 12mg alemtuzumab experienced idiopathic thromobocytopaenia (ITP) over the available follow up. The onset of idiopathic thromobocytopaenia mostly occurred after [redacted], [redacted] Serious cases of ITP were reported for [redacted] of patients. Nephropathy was observed in [redacted] of patients in the alemtuzumab group.

**Health-related quality of life**

4.19 The manufacturer assessed health related quality of life during the Phase II and III studies using the Short-Form Health Survey (SF-36), the Functional Assessment of Multiple Sclerosis (FAMS) and EuroQoL-5D (EQ-5D). In both treatment arms, baseline SF-36 and EQ-5D increased (i.e. quality of life improved) up to year 2 in CARE-MS I. In CARE-MS II patients treated with alemtuzumab had a [redacted] in health-related quality of life from baseline across all measures at all time points, whereas health-related quality of life did not increase with subcutaneous interferon beta-1a-treated from baseline on any health-related quality of life measure except at month 12 on the SF-36. Further, the improvement in quality of life from baseline [redacted] for patients receiving alemtuzumab than those receiving subcutaneous interferon beta-1a-treated on all health-related quality of life measures at most time points.

## *Evidence review group comments*

4.20 The Evidence Review Group (ERG) concluded that the manufacturer's reviews of the literature for evidence of the clinical and cost-effectiveness of alemtuzumab were well conducted, and that the manufacturer undertook a mixed-treatment comparison where direct evidence was lacking.

### Clinical trials and meta-analysis

4.21 The ERG considered that the 3 RCTs directly comparing alemtuzumab with interferon beta-1a (CARE-MS I, CARE-MS II and CAMMS223) were reasonably well conducted and provided evidence for the treatment effect of SAD, rate of relapse and adverse events. The ERG stated that the baseline characteristics appear to be similar between the two intervention groups in the three studies and that the populations in the trials were typical of those people with RRMS who are likely to receive DMTs in the UK. The ERG noted that there were some differences in participants between the studies owing to differences in the inclusion criteria. The CARE-MS II study included participants who had received DMTs previously, while participants in CAMMS223 and CARE-MS I were treatment naïve. All three trials also included participants who did not meet the inclusion criteria. The manufacturer's explanation was that while it recruited patients who had 2 relapses in the previous 2 years, some patients had episodes that did not fulfil the protocol definition of a relapse. The ERG noted that the manufacturer adjusted its analysis to account for this change from the protocol. The ERG considered that the manufacturer had not performed a true ITT analyses for the primary efficacy analysis on the two CARE MS studies, but rather analysed only those patients receiving at least one dose of medication. Clarification on this point received from the manufacturer confirmed that the primary efficacy analyses of all three trials used only patients who were randomised and received at least one dose ('full analysis set'). According to the manufacturer's statistical analysis plans for the 3 trials, analysis of the co-primary endpoints would be performed on the 'per-protocol set' (patients who had no major protocol deviations or inclusion/exclusion criteria deviations) if the per protocol population was less than 90% of the full analysis population, as in CAMMS223 [redacted] and CARE-MS II [redacted].Therefore analyses of the co-primary endpoints (and possibly other endpoints) were based on the per-protocol set, which the ERG considered to be an incomplete data set. Additionally, the ERG noted that the manufacturer did not present, discuss or interpret whether the results

were clinically meaningful, nor did it discuss or justify the clinically important differences between RCTs.

4.22 This ERG noted that the manufacturer's subgroup analysis for the rapidly evolving severe RRMS population using data from the CAMMS223 and CARE-MS II studies used a different definition of rapidly evolving severe RRMS than the one in the licensed indication and NICE guidance for natalizumab (NICE 2007): ≥ 2 disabling relapses in one year with ≥1 gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

4.23 The ERG reviewed the manufacturer's meta-analyses of the CAMMS223, CARE-MS I and II studies trials. The ERG stated that it was not appropriate to combine the studies because of differences in the populations. Two of the studies included treatment-naïve participants with an duration of MS of between 3 years (CAMMS223) and 5 years (CARE-MS I), while CARE-MS II included people previously treated with beta interferon or glatiramer acetate whose disease had recently relapsed. There were also differences in the inclusion criteria among the populations: CARE-MS II (EDSS 0.0 to 5.0), CAMMS223 and CARE-MS I (both EDSS 0.0 to 3.0) including pattern of recent relapses: CAMMS223 (≥2 relapses in the 2 years prior to the study), CARE-MS I and CARE-MS II (≥2 relapses in the 2 years prior to the study and at least 1 episode in the previous year, with objective neurological signs). While the manufacturer acknowledged that CARE-MS II had treatment-experienced patients with a greater time since their first ever relapse compared with the other studies, it did not explore this difference in sensitivity analyses. The ERG commented that the manufacturer did not present its fixed effects meta-analyses in its submission and that it poorly described the methods. Furthermore, the ERG noted that the manufacturer included no subgroups in its meta-analysis or sensitivity analysis of the different populations (for example, treatment naïve compared to previously treated).

### Mixed treatment comparison

4.24 The ERG stated that the methods of the manufacturer's MTC were reasonable, although it was not clear how the manufacturer finalised its list of included trials, or whether results of the analyses are robust to variations in trial populations. The ERG noted that the manufacturer did not judge the methodological quality of studies included in its MTC, and commented that it variably reported difference in baseline characteristics between studies.

4.25 The ERG commented that excluding from the MTC trials recruiting patients before 2000 had the effect of excluding all the direct evidence for subcutaneous interferon beta-1a and interferon beta 1-b versus placebo. The ERG compared the manufacturer's base case MTC (studies beyond year 2000) and its 'all years' MTC sensitivity analyses with the direct trial evidence from individual studies included in the MTC for SAD that last for 3 months (see Table 4). The ERG found differences in the hazard ratios estimated for subcutaneous interferon beta-1a and interferon beta 1-b with alemtuzumab. For subcutaneous interferon beta-1a, the credible range is reduced in the 'all trials' MTC analysis with the upper limit of the 95% credible interval no longer exceeding one. For interferon beta 1-b compared with alemtuzumab, a statistically non-significant harm in the base case is reversed to a small statistically non-significant benefit.

**Table 4 SAD lasting 3 months; comparison of hazard ratios from base case MTC, All Years MTC and direct evidence compared with placebo**

| Alemtuzumab 12 mg vs. … | Base case MTC | All trials MTC | Direct |
|---|---|---|---|
| Placebo | [redacted] | [redacted] | None |
| IFNβ-1b 250 µg | [redacted] | [redacted] | 0.68 (0.4 – 1.17) |
| IM IFNβ-1a | [redacted] | [redacted] | None |
| SC IFNβ-1a | [redacted] | [redacted] | 0.65 (0.45 – 0.94) |
| GA 20 mg | [redacted] | [redacted] | 0.93 (0.65 – 1.32) |
| Fingolimod 0.5 mg | [redacted] | [redacted] | 0.76 (0.61 – 0.94) |
| Natalizumab 300 mg | [redacted] | [redacted] | 0.58 (0.28 – 1.19) |
| µg – microgram, IFNβ- interferon beta, IM– intramuscular, SC – subcutaneous, GA – glatiramer acetate. | | | |

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

# 5 Comments from other consultees

5.1 The professional organisations stated that treating RRMS includes treating relapses, treating symptoms and treating with disease modifying drugs. The patient organisations commented on the limitations of the currently available treatments, stating that people with MS sometimes do not start or continue treatment with DMTs because of the side effects and anxiety about injections. The professional organisations stated that the position of alemtuzumab in the treatment pathway would depend on the marketing authorisation it receives.

5.2 Patient organisations stated that they expect alemtuzumab to reduce relapses, reduce disability progression, reduce administration of corticosteroids and hospital admission, improve quality of life and symptom control, and increase independence. The professional organisations stated that although fewer and less frequent injections or infusions may appeal to patients, some may not have considered the monitoring requirements involved following treatment with alemtuzumab. Compliance with monitoring requirements is a concern, considering that the side effects profile for alemtuzumab is more significant than some other treatments available. It is also unclear who would undertake the role of monitoring, which would likely require specialist nursing input. The professional organisations stated that the schedule for alemtuzumab monitoring (2 neurology visits in the first year, and 1 thereafter) is too infrequent to be safe. Monitoring should more closely resemble the monitoring protocol used in the clinical trials (e.g. 3 monthly visits for years 1 and 2, 6 monthly visits for years 3 and 4, and annual visits thereafter).

5.3 Patient and professional groups commented that MS treatment with disease modifying treatments is guided by national criteria (ABN 2001/2009 and NICE guidance), but that significant variation continues to exist across the UK because of the interpretation of guidelines and resource availability. Currently, alemtuzumab is available only in larger acute settings within specialist centres. If it were made available in local acute settings there would be more opportunity for patients to be treated closer to home. This could improve outcomes as community based specialist teams could be integrated into the support system for alemtuzumab treatment and monitoring.

# 6 Cost-effectiveness evidence

6.1 The manufacturer provided a de novo model to estimate the cost effectiveness of alemtuzumab for adults with active RRMS. The model was a multi-state Markov model simulating the course of MS for patients on different therapies, and incorporating health states for type of MS (RMSS or SPMS) and health states for severity defined by level of disability (EDSS scores 0-, [normal neurological examination] to 9 [confined to bed]). Patients with RRMS could enter the model in EDSS states 0-7. An ‘absorbing state’ of EDSS 10 represented death. In each cycle, patients remained in the same state, progressed to a worse state (moving to a better state was not possible), transferred to a state reflecting secondary progressive MS (SPMS), or died. The manufacturer assumed that when a patient progresses from RRMS to SPMS, the patient’s EDSS state increases by 1 point. The cycle length was 1 year, and the time horizon was a lifetime time horizon, assumed to be 50 years. Patients entering the model had a mean age of 39.3 years with approximately 3 times as many women and men. The analyses used an NHS and PSS perspective and applied a 3.5% discount rate on costs and health effects. The majority of patients received only two courses of alemtuzumab, but some patients received more (see section below on costs).

6.2 The natural history matrix for active RRMS and SPMS patients came from real-world longitudinal observational data on disability progression obtained from the London Ontario data set. Since no data for patients with EDSS of 0 were available in this data set, the manufacturer obtained transition probabilities for EDSS 0 from the placebo arms of the teriflunomide trials TOWER and TEMSO. In sensitivity analysis, the manufacturer used transition probabilities derived directly from patient level data of two of the alemtuzumab trials (CARE-MS I and CARE-MS II). The population entering the model was based on the average demographic profile of patients from the UK Risk Sharing Scheme; mean EDSS of patients with RRMS (85.5%) is 3.1, mean EDSS of patients with SPMS (14.5%) is 5.5. The model assumed that this data represented a 100% RRMS population.

6.3 To model the effect of treatment on the disease, the hazard ratios from the 3 month SAD outcome from the base case (studies from 2000) MTC were applied to the natural history matrix to generate a transition probability matrix between EDSS states. Separately, the manufacturer considered treatment effects on relapse in terms of frequency (relapse rates) and severity (whether or not the relapse leads to hospitalisation). In the base case, patients discontinued treatment if they converted from the RRMS to SPMS states, or progressed to EDSS state 7. On discontinuing treatment, patients were assumed to receive BSC only. In the model, it was assumed that no patients receiving alemtuzumab withdrew from treatment, whereas patients could withdraw from comparator treatments in any year (and subsequently receive best supportive care). The model assumed that the treatment effect of alemtuzumab does not wane over time (even during years when a patient is not receiving alemtuzumab), until a patient reached EDSS 7 or converted to SPMS when the benefit of having received alemtuzumab stopped, independent of the number of courses of alemtuzumab given. In each cycle patients could stop using comparators, discontinue treatment after reaching the EDSS 7, or experience relapse and adverse events. The probability of death was

dependent on the EDSS state (the higher the EDSS stage, the higher the risk of death), age and ratio of women to men. Table 6summarises the sources for the transition probabilities, discontinuation rates, relapse rates, and adverse event rates in the model.

**Table 5 Source of the manufacturer's model inputs**

| Model input | Source (in base case) | Source (sensitivity analyses) |
|---|---|---|
| Clinical and demographic profile of patients with RRMS entering the model<br>(EDSS score, age, sex) | • UK risk sharing scheme (Pickin et al. 2009) | • CARE-MS I AND CARE-MS II |
| 'Natural' disease progression of people not receiving DMT<br>(transition rates between EDSS states, conversion rate from RRMS to SPMS) | • Longitudinal observational data on disability progression from the London Ontario data set (1989) for most values<br>• Placebo arms of TOWER and TEMSO used for transition rate from EDSS 0 | • Transition probabilities derived directly from patient level data of 2 pivotal alemtuzumab trials CARE-MS I and CARE-MS II |
| Disease progression on alemtuzumab or other DMT (treatment effect)<br>(transition rates between EDSS states, conversion rates from RRMS to SPMS) | • Adjusted the natural history transition matrix by the relative treatment effect (3-month SAD) derived from the manufacturer's MTC<br>• No treatment effect applied to RRMS to SPMS conversion rates (conversion rates dependent on EDSS states) | • 'All years' MTC |
| Relapses<br>Relapse rate and severity (whether or not relapse leads to hospitalising patient) within each EDSS state | • Held et al. 2005 (relapse rate per year since diagnosis) and Orme et al 2007 UK MS survey (applied to Held et al. to estimate the annual relapse rate for each EDSS state)<br>• Dee at el. 2012 used to estimate the proportion of relapses that lead to hospitalisation | • Patzold et al 1982 and Orme et al 2007 |
| Relapses (treatment effect) | • MTC used to estimate annualised relapse rates<br>• Hospitalisation due to relapse (data applied to base rate): | • 'All years' MTC used to estimate annualised relapse rates |

| | | |
|---|---|---|
| | • Alemtuzumab: CARE-MS II<br>• Rebif 44 µg and fingolimod: data from individual trials<br>• Betaferon, Rebif 22 µg, Avonex, glatiramer acetate: assumed same as Rebif 44 µg<br>• Fingolimod: weighted average from 3 trials<br>• Natalizumab: assumed same as fingolimod | |
| Discontinuation/withdrawal rates<br>(all cause, for all treatments) | • Base case MTC<br>• For alemtuzumab, manufacturer assumed the impact from withdrawing to have no effect and was therefore not modelled explicitly | • 'All years' MTC |
| Mortality<br>(per EDSS state, irrespective of whether its RRMS or SPMS) | • Used the all-cause mortality rates of the UK general population (England and Wales life tables 2008-2010) and applied a relative increase per EDSS state. EDSS 0 is not associated with an increased mortality risk.<br>• Mortality rate increase with EDSS state estimated from Pokorski et al. 1997 | • n/a |
| Adverse events | • MTC data (rather than using the restricted MTC, used all-years MTC)<br>• Captured AEs that had a ≥4% difference in occurrence compared with placebo | • Adverse event probability in all years, 80% RRMS equal to probability for year 1 |

6.4 The manufacturer's model applied utility values to each of the EDSS states (Table 7). Generally, utility values decrease as EDSS scores increase. However, the utility value for EDSS 3 was lower than EDSS 4. The manufacturer collected EQ-5D data in the CARE MS-I and II studies but did not apply these data in the model noting that they were not available at the time of submission. Instead, the manufacturer drew utility

values for the EDSS states from Orme et al (2007) which was a UK survey of health related quality of life in (EQ-5D) in people with MS. Of note, EDSS states 8 and 9 had negative utility values indicating a state worse than death. The manufacturer applied disutilities for a relapse, to caregivers, and for adverse events. The disutility for relapse was estimated from Orme et al. 2007, and a US study (Prosser et al 2003) was used to estimate the disutility for relapse leading to hospitalisation. To estimate disutility to caregivers, the manufacturer used values taken from a study by Gani et al. (2008) and the manufacturer estimated the time spent caring for the patient from Orme et al. For disutility values applied for each adverse event, as summarised in Table 7, the manufacturer obtained values annualising disutility from the published literature. The manufacturer further took into account how long each adverse event lasted, and was treatment specific. The adverse events included infusion associated reactions, bronchitis, herpes zoster, urinary tract infections, autoimmune thyroid related adverse events, nephropathies, ITP, other cytopaenias and vomiting.

**Table 6 Utility values (applied per annual cycle) in the manufacturer's model**

| **State** | **Expanded disability status scale (EDSS) score** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **0** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** |
| Relapsed remitting multiple sclerosis | 0.870 | 0.799 | 0.705 | 0.574 | 0.610 | 0.518 | 0.460 | 0.297 | −0.049 | −0.195 |
| Secondary progressive multiple sclerosis | 0.045 less than relapsed remitting multiple sclerosis | | | | | | | | | |
| Caregiver disutility | 0.000 | −0.001 | −0.003 | −0.009 | −0.009 | −0.020 | −0.027 | −0.053 | −0.107 | −0.140 |
| Relapse disutility (without hospitalisation) | -0.071 (without hospitalisation) and -0.2356 (with hospitalisation) | | | | | | | | | |
| Infusion-associated reaction | −0.0002 (alemtuzumab) | | | | | | | | | |
| Bronchitis | −0.0004 (alemtuzumab) | | | | | | | | | |
| Herpes zoster | −0.0046 (alemtuzumab) | | | | | | | | | |
| Urinary tract infection | −0.0039 (alemtuzumab, natalizumab) | | | | | | | | | |
| Autoimmune | −0.1081 (alemtuzumab) | | | | | | | | | |

| | |
|---|---|
| thyroid-related adverse event | |
| Nephropathies | −0.8700 (alemtuzumab) |
| ITP overall | −0.0065 (alemtuzumab) |
| Cytopaenias | −0.0000 negligible (alemtuzumab) |
| Vomiting | −0.0020 (alemtuzumab) |

Adapted from tables B7.4.2 and B7.4.4 of the manufacturer's submission

6.5 The costs applied in the manufacturer's model are summarised in Table 8 and Table 9. For alemtuzumab, the manufacturer's base case assumes that [redacted] of patients received a subsequent dose in year 3 in line with the CAMMS 223 extension study data, [redacted] in years 4 and 5, and [redacted] annually beyond 5 years. The model used NHS reference costs and the payment by results (PbR) tariff to estimate the costs of adverse events associated with each treatment (see Table 10). Although the SmPC states that patients would receive only 4 years of monitoring following their last treatment course of alemtuzumab, in the model monitoring for alemtuzumab was assumed to last for up to 12 years. Some costs were derived from the literature; health state costs (including direct medical costs and direct non-medical costs) were derived from Tyas et al 2007 (a UK study), and the cost associated with relapse from Dee at al 2012 (an Ireland study). An alternate source (Karampampa et al. 2012, a UK study) was used to derive health state costs for a sensitivity analysis although it provides only aggregated natural history costs for EDSS 0-3, 4-6 and 7-9, rather than costs per individual EDSS state. The resource use and costs applied in the model were validated by the manufacturer's clinical experts. The cost of fingolimod reflected a simple discount through a patient access scheme agreed with the Department of Health. However, the manufacturer did not have access to the magnitude of this discount and therefore could not use it in its base case analysis (but instead explored different prices of fingolimod in sensitivity analysis, using a range of discounts).

**Table 7 Annual costs associated with technologies in the manufacturer's model**

| Treatment | Acquisition cost (£) | | Administration cost (£) | | Monitoring cost (£) | | Total (£) | |
|---|---|---|---|---|---|---|---|---|
| | Year 1 | Year 2+ | Year 1 | Year 2+ | Year 1 | Year 2+ | Year 1 | Year 2+ |
| Alemtuzumab* | 35,225 | 21,135 | 2,438 | 1,487 | 443 | 274 | 38,106 | 22,896 |
| SC IFNβ-1a 44µg | 8,942 | 8,942 | 174 | 0 | 355 | 346 | 9,471 | 9,288 |
| SC IFNβ-1a 22µg | 7,513 | 7,513 | 174 | 0 | 355 | 346 | 8,042 | 7,859 |
| IM IFNβ-1a | 8,502 | 8,502 | 174 | 0 | 355 | 347 | 9,031 | 8,849 |
| IFNβ-1b | 7,259 | 7,259 | 174 | 0 | 355 | 347 | 7,788 | 7,606 |
| Glatiramer acetate | 5,823 | 5,823 | 174 | 0 | 338 | 338 | 6,335 | 6,161 |
| Fingolimod** | 19,163 | 19,163 | 474 | 0 | 642 | 347 | 20,278 | 20,001 |
| Natalizumab | 14,730 | 14,730 | 6162 | 6162 | 493 | 493 | 21,385 | 21,385 |

*List price is to be confirmed with the Department of Health.

**A commercial in confidence PAS is available to the UK NHS for fingolimod. Therefore, sensitivity analyses considered a number of potential PAS prices for fingolimod ranging from £11,000 to £15,000 per annum.

**Table 8 Health state costs (applies to RRMS and SPMS, Tyas et al) included in the manufacturer's model**

| Health states (applies to RRMS and SPMS) | Base case value (£) [Tyas et al. 2007] | Sensitivity analysis value (£) [Karampampa, 2012] |
|---|---|---|
| EDSS 0 | 5671 | 3579 |
| EDSS 1 | 5980 | 3579 |
| EDSS 2 | 7134 | 3579 |
| EDSS 3 | 10881 | 3579 |
| EDSS 4 | 7756 | 14171 |
| EDSS 5 | 11545 | 14172 |
| EDSS 6 | 12837 | 14172 |
| EDSS 7 | 24357 | 49662 |
| EDSS 8 | 34617 | 49662 |

| Health states (applies to RRMS and SPMS) | Base case value (£) [Tyas et al. 2007] | Sensitivity analysis value (£) [Karampampa, 2012] |
|---|---|---|
| EDSS 9 | 32619 | 49662 |
| EDSS 10 | 0 | 0 |

**Table 9 Costs of treatment of DMT adverse events**

| Adverse events | Associated cost | Unit Cost |
|---|---|---|
| Infusion-associated reaction | Administered in hospital | £0.00 |
| Autoimmune thyroid-related adverse event | Costs per "cure" analysis with initial treatment Radioiodine. In the clinical trials less than 1% received surgical intervention (see Section B6.9) | £1,833 |
| Nephropathies | 1 GP consultation, 1 nephrologist consultant visit, 3 doses of Cyclophosphamide (500 mg), 3 doses of IV methylprednisolone (1 g) and 1 month of oral methylprednisolone | £339 |
| ITP (treatment with steroids only) | Based on cost of thrombocytopenia, 2 doses of IV methylprednisolone 1g and daily oral methylprednisolone 16mg for one month | £1,329 |
| ITP (treatment with steroids, IVIG) | Based on cost of thrombocytopenia, immunoglobulin 1 g/kg/d for 2 days assuming 75kg adult, 2 doses of IV methylprednisolone 1g and daily oral methylprednisolone 16mg for one month | £7,029 |
| ITP (treatment with steroids, tranexamic acid, platelets, rituximab, IVIG) | Based on cost of thrombocytopenia, immunoglobulin 1 g/kg/d for 2 days assuming 75kg adult, 2 doses of IV methylprednisolone 1g and daily oral methylprednisolone 16mg for one month<br>Rituximab 375mg/m2 once a week for 4 weeks, assuming average male is 1.7m2 – dose = 638mg | £12,132 |
| ITP (treatment with steroids, platelets, rituximab) | Based on cost of thrombocytopenia, 2 doses of IV methylprednisolone 1g and daily oral methylprednisolone 16mg for one month<br>Rituximab 375mg/m2 once a week for 4 weeks, assuming average male is 1.7m2 – dose = 638mg | £6,427 |
| ITP (treatment with steroids, platelets, IVIG) | Based on cost of thrombocytopenia, 2 doses of IV methylprednisolone 1g and daily oral methylprednisolone 16mg for one month | £7,237 |
| Severe infection | Weighted cost based on FREEDOMS trial [Kappos et al. 2010] of respiratory infection (67%) [GP consultation and respiratory infection], herpes infection (10%) [GP consultation and minor skin disorder], influenza-like infection (15%) [2 GP consultations and viral infection] and UTI (9%) [GP consultation and trimethoprim]. | £582 |
| PML | Cost of non-elective inpatient (long-stay), MRI scan, JC virus PCR and Lumbar Puncture from natalizumab manufacturer submission | £2,959 |
| Anaphylactic and anaphylactoid reactions | Hospitalisation | £362 |
| Atrioventricular block, first degree | Hospitalisation | £818 |
| Atrioventricular block, second degree | Hospitalisation | £1,357 |

6.6 The manufacturer's base case analyses compared alemtuzumab with subcutaneous interferon beta-1a 44µg, as it was the most effective treatment among the comparators according to the manufacturer's MTC

results, and was the comparator in the alemtuzumab trials. The manufacturer also conducted a full incremental analysis, comparing alemtuzumab with the individual treatments: glatiramer acetate, subcutaneous interferon beta-1a 22 µg, subcutaneous interferon beta-1a 44µg, intramuscular interferon beta-1a, interferon beta-1b, fingolimod and natalizumab. Additionally, the manufacturer provided separate analyses of alemtuzumab compared with fingolimod and with natalizumab for the RRMS and the HA and RES subgroups, respectively.

6.7 The manufacturer's probabilistic base case considered an incremental analysis and compared all treatments for active RRMS ranking each treatment by cost (Table 11). The mean probabilistic sensitivity analysis results suggested that

- alemtuzumab dominated interferon beta-1b, fingolimod (without PAS), fingolimod (assuming a PAS price of £13,000 per year) and natalizumab;
- Intramuscular interferon beta-1a was dominated by subcutaneous interferon beta-1a 44µg; and
- alemtuzumab extendedly dominated subcutaneous interferon beta-1a 44µg and subcutaneous interferon beta-1a 22µg.

6.8 The remaining comparison between alemtuzumab and glatiramer acetate showed an incremental cost-effectiveness ratio (ICER) of £7,017 per QALY. The manufacturer's deterministic results found similar results, and a similar ICER for alemtuzumab of £8,924 per QALY compared with glatiramer acetate. In both of the subgroup analyses (comparing alemtuzumab with fingolimod for highly active RRMS and alemtuzumab with natalizumab for rapidly evolving severe RRMS) the cost effectiveness of alemtuzumab dominated the comparator treatments.

**Table 10 Manufacturer's incremental probabilistic base case including alemtuzumab and all comparators ordered by increasing total costs**

| Technologies | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs | ICER (£) versus baseline (QALYs) | ICER (£) incremental (QALYs) |
|---|---|---|---|---|---|---|
| Glatiramer acetate | 484,590 | 2.887 | | | | |
| SC IFNβ-1a 44µg | 487,368 | 2.923 | 2,778 | 0.036 | 77,453 | 77,453 |
| SC IFNβ-1a 22µg | 487,642 | 3.034 | 3,052 | 0.147 | 20,713 | 2,459 |
| IM IFNβ-1a | 492,860 | 2.872 | 8,270 | -0.014 | Dominated | Dominated |
| Alemtuzumab | 494,319 | 4.273 | 9,729 | 1.386 | 7,017 | 1,042 |
| IFNβ-1b | 497,009 | 2.632 | 12,420 | -0.255 | Dominated | Dominated |
| Fingolimod (assumed PAS price £13,000) | 506,377 | 3.089 | 21,788 | 0.202 | 107,778 | 20,503 |
| Natalizumab | 510,726 | 3.434 | 26,136 | 0.547 | 47,757 | 12,599 |
| Fingolimod | 528,570 | 3.106 | 43,980 | 0.220 | 200,200 | Dominated |

**Table 11 Manufacturer's incremental deterministic base case including alemtuzumab and all comparators ordered by increasing total costs**

| Technologies | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs | ICER (£) versus baseline (QALYs) | ICER (£) inc (QALYs) |
|---|---|---|---|---|---|---|
| Glatiramer acetate | 487,842 | 2.745 | | | | |
| SC IFNβ-1a 44µg | 489,354 | 2.850 | 1,512 | 0.106 | 14,277 | Extendedly dominated |
| SC IFNβ-1a 22µg | 490,388 | 2.854 | 2,545 | 0.110 | 23,227 | Extendedly dominated |
| IM IFNβ-1a | 494,626 | 2.764 | 6,784 | 0.019 | 354,272 | Dominated |
| Alemtuzumab | 499,347 | 4.034 | 11,505 | 1.289 | 8,924 | 8,924 |
| IFNβ-1b | 502,969 | 2.329 | 15,127 | -0.416 | Dominated | Dominated |
| Fingolimod (assumed PAS price £13,000) | 507,049 | 3.068 | 19,207 | 0.323 | 59,443 | Dominated |
| Fingolimod | 529,094 | 3.068 | 41,252 | 0.323 | 127,672 | Dominated |
| Natalizumab | 530,800 | 3.373 | 42,958 | 0.628 | 68,383 | Dominated |
| SC – subcutaneous, IFNβ –interferon beta, IM – intramuscular | | | | | | |

6.9 The manufacturer conducted one-way sensitivity analyses which showed that the cost effectiveness of alemtuzumab was most sensitive to the hazard ratios reflecting the magnitude of the comparative effectiveness of treatment with alemtuzumab for sustained disability progression, disease costs, and rate of discontinuing subcutaneous interferon beta-1a 44µg. Factors that minimally affected the ICERS included, among others, disutility of adverse events, whether or not relapses lead to hospitalisations, annualised response rates, and using EQ-5D utilities. For each of the analyses alemtuzumab continued to dominate most comparators (glatiramer acetate is the exception), apart from when the hazard ratios for disability progression were varied. When applying the lower 95% confidence interval for the subcutaneous interferon beta-1a 44µg disability progression hazard ratio, the resulting ICER was £24,668 per QALY gained. When applying values reflecting the upper 95% confidence interval for the hazard ratio associating alemtuzumab and sustained disability progression, the ICER for alemtuzumab compared with the subcutaneous interferon beta-1a 44µg was £1,200,973 per QALY gained. Alemtuzumab dominated fingolimod when applying the lower 95% confidence interval for alemtuzumab, but was dominated when the upper 95% confidence interval for alemtuzumab was applied (resulting in higher costs and lower QALYs).

6.10 The manufacturer also tested the sensitivity of the incremental deterministic analysis to the choice of MTC by using the ‘all years’ MTC data and to the percentage of people with RRMS (by using 100% RRMS compared to ≥80% RRMS). When using the ‘all years’ data and 100% RRMS, the ICER for alemtuzumab was £27,434 per QALY gained. Using the post 2000 data and 100% RRMS, the ICER for alemtuzumab was £10,822 and when using the ‘all years’ data and 80% RRMS, the ICER for alemtuzumab was £9982 per QALY gained.

6.11 The manufacturer conducted a number of additional scenario analyses using subcutaneous interferon beta-1a 44µg as the comparator. In these,

the ICER for alemtuzumab ranged between £221 and £20,388 per QALY gained or dominated. The following were investigated:

- Baseline characteristics sourced from CARE-MS trials
- Costs related to the natural history of MS from Karampampa, 2012 - alemtuzumab dominates subcutaneous interferon beta-1a 44 µg
  - The costs from Karampampa are lower than the base case for EDSS states 0-3, but higher for the more severe EDSS states.
- Natural history transition probabilities for 100% RRMS
- Long-term treatment effect 25% waning after year 5 for all treatments
- Long-term treatment effect 50% waning after year 5 for all treatments
- No treatment effect on relapses or proportion leading to hospitalisation
- No discounting of costs or outcomes
- 6% discounting of costs and outcomes
- Using direct comparison method: transition probabilities derived directly from pooled CARE-MS I and CARE-MS II - - alemtuzumab dominates subcutaneous interferon beta-1a 44 µg
- Treatment of SPMS with SC IFNβ-1a 44µg assuming 50% efficacy
- Duration of autoimmune disease 10 years

### *Evidence review group comments*

6.12 The ERG reviewed the manufacturer's model and economic systematic review. The ERG commented that the manufacturer undertook a comprehensive, well rounded systematic literature review and provided a de novo cost effectiveness model that was flexible to sensitivity and scenarios analyses. The ERG commented that the structure of the manufacturer's economic model was consistent with the currently accepted theory of MS and previous economic evaluations of treatments for MS, that the methods of analysis were appropriate and conform to NICE methodological guidelines

6.13 The ERG noted that the manufacturer conducted a systematic review to identify the most appropriate transition matrix to reflect the natural history

for disability progression of MS, but that the ERG was unable to find any more appropriate data thus concluding that the London Ontario dataset was the most appropriate, robust and clinically plausible. However, the ERG commented that the manufacturer did not fully explore the uncertainty of using this dataset and, in light of previous technology appraisals, the alternative data sources should have been explored more extensively and validated, where possible, against trial data.

6.14 The ERG evaluated the external consistency of the economic model outputs as compared to published literature. The ERG noted that there is no validation beyond 2 years, and therefore there is some uncertainty as to the validity of longer term outcomes.

6.15 The ERG stated that the manufacturer performed appropriate structural sensitivity analyses and that the rationale for these analyses was reasonable. Some of these structural sensitivity analyses had been recommended in previous MS technology appraisals. The ERG considered that the sensitivity analyses completed were comprehensive, although the manufacturer did not conduct sensitivity analyses that varied the disease progression for best supportive care, or the rate of progression from RRMS to SPMS.

6.16 The ERG identified weaknesses and uncertainty in the manufacturer's economic analysis. The ERG stated that basing the starting model population on the UK risk sharing scheme instead of the clinical trials populations introduced uncertainty into the model, as these populations did not have the same baseline characteristics. The ERG also commented that the distribution of initial EDSS among the hypothetical population used in the model was not appropriate, as it did not reflect the trial population. The ERG commented that the conversion rate used for patients transitioning from RRMS to SPMS was too high. The ERG also stated that the London Ontario estimates for disease progression for patients not taking DMT did not allow patient to improve in EDSS score, unlike trial based transition probabilities, although the ERG commented

that using the trial data could be problematic as it was based on a short period of time. The ERG varied these assumptions in their additional analyses.

**Exploratory sensitivity analyses undertaken by the ERG**

6.17 The ERG conducted exploratory analyses to address the issues and uncertainties raised in its critique of the manufacturer's cost effectiveness analyses. The ERG presented a 'preferred' base case that included alternative characteristics for the patient population, and a different progression rate from RRMS to SPMS (Table 13). The ERG conducted a series of sensitivity analyses to test the uncertainties that arose in the ERG critique of the manufacturer's model.

6.18 The ERG considered that the pooled trial population from the CARE-MS trials is the most relevant population because these represented all patients with RRMS, instead of only those patients that would otherwise be treated with DMTs. The ERG used a modified incremental cost effectiveness analysis where alemtuzumab was compared with subcutaneous interferon beta-1a 44 µg as the most relevant comparator because it was the direct comparator in the clinical trials and it was the most efficacious in the MTC. Using the baseline characteristics for the CARE-MS trials patients, the ERG calculated that the ICER for alemtuzumab compared with subcutaneous interferon beta-1a 44 µg reduces from £8445 (manufacturer's base case) to £2865 per QALY gained for its preferred base case. The ERG also considered that applying a conversion rate of 15 years from RRMS to SPMS (instead of the 10-11 years from RRMS to SPMS used by the manufacturer) was appropriate, as used in the NICE Technology Appraisal Teriflunomide for the treatment of RRMS. This has the effect of reducing the ICER to £3100 per QALY gained for alemtuzumab compared with subcutaneous interferon beta-1a 44 µg. The ERG's preferred approach which combines these changes results in alemtuzumab dominating subcutaneous interferon beta-1a 44 µg.

**Table 12 Comparison of manufacturer's base case with ERG's preferred scenarios (alemtuzumab versus subcutaneous interferon beta-1a 44µg)**

| Technologies | SC IFNβ-1a 44µg | | Alemtuzumab | | | | |
|---|---|---|---|---|---|---|---|
| | **Total costs (£)** | **Total QALYs** | **Total costs (£)** | **Total QALYs** | **Incr. costs (£)** | **Incr. QALY s** | **ICER (£) inc. (QALYs)** |
| Manufacturer's base case | 489,354 | 2.850 | 499,347 | 4.034 | 9,993 | 1.183 | 8,445 |
| CARE-MS trials characteristics | 439,732 | 4.894 | 444,226 | 6.460 | 4494 | 1.566 | 2,869 |
| Reduced progression RRMS to SPMS | 480,755 | 3.083 | 485,379 | 4.575 | 4624 | 1.492 | 3,100 |
| Combined | 431,896 | 5.205 | 430,241 | 7.147 | -1655 | 1.942 | dominated |

6.19 Although best supportive care was not in the NICE scope, the ERG included it an exploratory incremental deterministic analyses for context. Data for best supportive care was available in the manufacturer's model. The results using the ERG's preferred parameters show that alemtuzumab dominates all comparative treatments compared to best supportive care with an ICER of £9907 per QALY gained (see Table 14)

**Table 13 ERG's exploratory incremental deterministic analyses including best supportive care as a comparator**

| Technologies | Total costs (£) | Total QALYs | Inc costs (£) vs BSC | Inc QALYs vs BSC | ICER (£) inc (QALYs) |
|---|---|---|---|---|---|
| Best supportive care | 408,040 | 4.906 | - | - | - |
| Alemtuzumab | 430,241 | 7.147 | 22,201 | 2.241 | 9907 |
| Glatiramer acetate | 430,635 | 5.065 | 22,595 | 0.159 | Dominated |
| SC IFNβ-1a 44µg | 431,896 | 5.205 | 23,856 | 0.299 | Dominated |
| IM IFNβ-1a | 440,185 | 5.089 | 32,145 | 0.183 | Dominated |
| IFN | 453,837 | 4.431 | 45,797 | -0.475 | Dominated |
| Fingolimod | 492,053 | 5.539 | 84,013 | 0.633 | Dominated |
| Natalizumab | 493,466 | 5.962 | 85,426 | 1.056 | Dominated |
| SC – subcutaneous, IFNβ –interferon beta, IM – intramuscular, | | | | | |

6.20 The ERG's preferred base case was tested in sensitivity analyses for alemtuzumab versus subcutaneous interferon beta-1a 44 µg for uncertainties that arose in the ERG critique of the manufacturer's model. These sensitivity analyses, shown in Table 15, included:

- reducing the transition probabilities to more severe health states from the London Ontario dataset by 50%
- Quality of life utility values (upper and lower confidence intervals from the Orme and colleagues data used in the manufacturer's model)
- Disease health state costs from Karampampa *et al.* 2012
- Disease health states costs from Biogen *et al*.2007
- Relapse cost for hospitalisation, £3039
- Waning treatment effect, years 10+ 75%
- Waning treatment effect, years 6-9 75%, year 10+ 50%
- Proportion of patients receiving subsequent alemtuzumab treatment at year 3 (60%) and years 5+ (20%)
- Mixed treatment comparison, 'all years', >80% RRMS
- Disease progression using SAD lasting for 6 months

The highest ICER from ERG's exploratory sensitivity analyses was £8336 which resulted from testing the sensitivity of the model to changes in the proportion who receive subsequent doses of alemtuzumab. The ERG used 60% as the proportion of the patients receiving subsequent doses of alemtuzumab at year 3 and 20% at year 5 and beyond. Alemtuzumab continued to dominate subcutaneous interferon beta-1a in 6 of the 11 analyses.

**Table 14 ERG's exploratory sensitivity analyses for ERG's preferred base case**

| Technologies | SC IFNβ-1a 44 µg | | Alemtuzumab | | | | |
|---|---|---|---|---|---|---|---|
| Sensitivity Analysis | Total costs (£) | Total QALYs | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs | ICER (£) inc (QALYs) |
| ERG preferred base case | 431,896 | 5.205 | 430,241 | 7.147 | -1655 | 1.942 | -852[a] |
| 50% reduction in disease progression natural history | 406,905 | 6.109 | 406,121 | 8.018 | -784 | 1.909 | -411[a] |
| Quality of life utility values LCI | 431,896 | 1.088 | 430,241 | 3.090 | -1655 | 2.002 | -827[a] |
| Quality of life utility values UCI | 431,896 | 9.038 | 430,241 | 10.975 | -1655 | 1.937 | -855[a] |

| Technologies | SC IFNβ-1a 44 µg | | Alemtuzumab | | | | |
|---|---|---|---|---|---|---|---|
| Sensitivity Analysis | Total costs (£) | Total QALYs | Total costs (£) | Total QALYs | Inc costs (£) | Inc QALYs | ICER (£) inc (QALYs) |
| Disease health state costs from Karampampa *et al.* 2012[45] | 548,917 | 5.205 | 506,465 | 7.147 | -42,452 | 1.942 | -21,862[a] |
| Disease health states costs from Biogen *et al*.2007 | 248,579 | 5.205 | 257,617 | 7.147 | 9038 | 1.942 | 4,654 |
| Relapse cost for hospitalisation, £3039 | 423,393 | 5.205 | 425,360 | 7.147 | 1966 | 1.942 | 1,013 |
| Waning effect, years 10+ 75% | 432,150 | 5.193 | 435,268 | 6.911 | 3117 | 1.718 | 1,815 |
| Waning effect, years 6-9 75%, 10+ 50% | 432,843 | 5.162 | 443,079 | 6.560 | 10236 | 1.399 | 7,319 |
| % patients receiving alemtuzumab, year 3 60%, year 5+ 20% | 431,896 | 5.205 | 446,160 | 6.917 | 14263 | 1.711 | 8,336 |
| MTC All years, 80% RRMS | 428,073 | 5.341 | 422,632 | 7.524 | -5440 | 2.184 | -2,491[a] |
| Disease progression using SAD lasting 6 months | 437,211 | 4.936 | 426,446 | 7.333 | -10764 | 2.396 | -4,492[a] |
| [a] Alemtuzumab dominates subcutaneous interferon beta-1a 44 µg (is cheaper and more effective). | | | | | | | |

### Treatment naive and treatment experienced subgroups

6.21 The ERG considered it inappropriate to combine the results from the 3 studies because of differences in the baseline characteristics of the study populations. Therefore, the ERG explored the cost effectiveness for the treatment naïve and treatment-experienced subgroups separately using the ERG preferred base case and the relative risk for annualised rate of relapse and SAD lasting 3 months for alemtuzumab versus subcutaneous interferon beta-1a 44µg. The parameter values for subcutaneous interferon beta-1a 44µg are as in the base case and the annualised rate of relapse and SAD lasting for 3 months parameter values for alemtuzumab are estimated using the relative risks from the trials. In the treatment naïve group, alemtuzumab dominated subcutaneous interferon beta-1a 44µg using the effectiveness from the CAMS 223 trial and the cost

effectiveness was £6392 per QALY gained for alemtuzumab versus subcutaneous interferon beta-1a 44µg for the CARE MS I trial. Alemtuzumab dominated subcutaneous interferon beta-1a 44µg for a pooled analysis (ERG meta-analysis) of the two trials. For the treatment experienced group, using effectiveness data from CARE MS II, the cost effectiveness was £2854 per QALY gained for alemtuzumab versus subcutaneous interferon beta-1a 44µg. See Table 16.

**Table 15 ERG's exploratory subgroup analyses (all parameter values including efficacy data were used separately for no pooling of treatment naïve and experienced subgroups)**

| | SC IFNβ-1a 44µg | | Alemtuzumab | | | | |
|---|---|---|---|---|---|---|---|
| **Study** | **Total costs (£)** | **Total QALYs** | **Total costs (£)** | **Total QALYs** | **Incr. costs (£)** | **Incr. QALYs** | **ICER (£) inc. (QALYs)** |
| Treatment naïve | | | | | | | |
| CAMS 223 | 431,896 | 5.205 | 402,960 | 8.459 | -28937 | 3.253 | -8,894 (Dominated) |
| CARE MS I | 431,896 | 5.205 | 441,006 | 6.631 | 9110 | 1.425 | 6,392 |
| Pooled (CAM 223, CARE MS I) | 431,896 | 5.205 | 423,531 | 7.463 | -8365 | 2.257 | -3,705 (Dominated) |
| Treatment experienced | | | | | | | |
| CARE MS II | 431,896 | 5.205 | 436,592 | 6.851 | 4695 | 1.645 | 2,854 |

**RES and HA RRMS subgroups**

6.22 The ERG also reran separate MTC analyses and subgroup economic analyses for the HA RRMS despite interferon use and RES RRMS subgroups using the ERG's preferred base case for a slower progression from RRMS to SPMS for RES RRMS subgroup and different patient characteristics for the HA RRMS. These changes made only minimal changes to the model results and alemtuzumab continued to dominate fingolimod and natalizumab in these subgroup analyses.

6.23 In summary, the ERG tested the manufacturer's model in a series of sensitivity analyses and found the results robust to changes in

assumptions and input parameters, with a cost effectiveness of less than £10,000 per QALY compared to subcutaneous interferon beta-1a 44 µg for all its exploratory analyses.

# 7 Equality issues

7.1 No equality issues have been raised through the scoping process, or in any of the submissions.

# 8 Innovation

8.1 The manufacturer stated in their submission that alemtuzumab should be considered innovative because of the manner in which it is administered. According to the manufacturer, there are benefits that cannot be fully captured within the QALY calculation that alemtuzumab provides for both patients and carers due to its finite, annual administration schedule compared to other oral or parenteral therapies that are chronically and frequently administered.

# 9 Authors

**Richard Diaz**
Technical Lead

**Joanne Holden**
Technical Adviser

# Appendix A: Supporting evidence

## *Related NICE guidance*

### Published

- Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis. NICE technology appraisal guidance 254 (2012).
- Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis. NICE technology appraisal guidance 127 (2007).
- Management of multiple sclerosis in primary and secondary care. NICE clinical guideline 8 (2003).
- Beta interferon and glatiramer acetate for the treatment of multiple sclerosis. NICE technology appraisal guidance 32 (2002).

### Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Dimethyl fumarate for treating relapsing-remitting multiple sclerosis. NICE technology appraisal. Earliest anticipated date of publication January 2014.
- Teriflunomide for treating relapsing-remitting multiple sclerosis. NICE technology appraisal. Earliest anticipated date of publication January 2014.
- Laquinimod for treating relapsing-remitting multiple sclerosis. NICE technology appraisal. Earliest anticipated date of publication October 2014.

# Appendix B: Clinical efficacy section of the European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003718/WC500150522.pdf