Alemtuzumab for treating relapsing-remitting multiple sclerosis

Technology appraisal guidance
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Your responsibility

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1 Guidance

1.1 Alemtuzumab is recommended as an option, within its marketing authorisation, for treating adults with active relapsing–remitting multiple sclerosis.
2 The technology

2.1 Alemtuzumab (Lemtrada, Genzyme) is an antibody that binds to cells of the immune system (B and T cells), causing their destruction. The way in which alemtuzumab slows the decline of active relapsing–remitting multiple sclerosis is not fully understood. Alemtuzumab has a UK marketing authorisation for treating adults with relapsing–remitting multiple sclerosis with active disease defined by clinical or imaging features. The recommended dosage of alemtuzumab is 12 mg/day administered by intravenous infusion for 2 treatment courses. The initial treatment course lasts 5 consecutive days, followed 12 months later by the second treatment course of 3 consecutive days.

2.2 The summary of product characteristics lists the following adverse reactions for alemtuzumab: autoimmunity (immune thrombocytopenic purpura, thyroid disorders, nephropathies [kidney diseases or damage], cytopenias [reduced blood cell numbers]), infusion-associated reactions, rash, headache, fever and respiratory tract infections. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The price of alemtuzumab is £7045 per 12 mg vial, which equates to £56,360 for the full course of treatment consisting of 5 daily consecutive 12 mg doses in year 1, followed by 3 daily consecutive 12 mg doses 12 months later in year 2. Costs may vary in different settings because of negotiated procurement discounts.
3 The manufacturer’s submission

The Appraisal Committee’s remit was to appraise the clinical and cost effectiveness of alemtuzumab within its licensed indication for treating active relapsing–remitting multiple sclerosis. The Appraisal Committee (section 7) considered evidence submitted by the manufacturer of alemtuzumab and a review of this submission by the Evidence Review Group (ERG; section 8).

Clinical effectiveness

3.1 The manufacturer provided clinical-effectiveness evidence, identified by systematic review, from:

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

- 1 phase II randomised controlled clinical trial: CAMMS223 (n=334, maximum follow-up of 3 years extended by a follow-up period of 4 years from final alemtuzumab dose)

- 1 extension study: CAMMS03409 (n=1322, median follow-up of 7.1 years), which enrolled people with active relapsing–remitting multiple sclerosis from the CAMMS223, CARE-MS I and CARE-MS II trials. In this study, patients previously randomised to the control group in CAMMS223, CARE-MS I and CARE-MS II received alemtuzumab and patients previously randomised to alemtuzumab in CAMMS223, CARE-MS I and CARE-MS II received further treatment with alemtuzumab, as needed.

In addition, the manufacturer submitted a meta-analysis of the above-listed trials and a mixed treatment comparison to compare alemtuzumab with other disease-modifying treatments for active relapsing–remitting multiple sclerosis (see sections 3.7-3.8).

3.2 CARE-MS I, CARE-MS II and CAMMS223 compared the effectiveness of 12 mg alemtuzumab (with an additional arm receiving 24 mg per infusion in CAMMS223 only) with subcutaneous interferon beta-1a (Rebif, small initial doses, gradually increasing to 44 micrograms 3 times weekly). All 3 trials included sites in the UK. All 3 trials specified the number of previous relapses patients must have had before they could enrol. For CAMMS223 this was at least 2 relapses in the previous 2 years. 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. CARE-MS I and CAMMS223 included patients with an Expanded Disability Status Scale (EDSS) score between 0 and 3 (in which 0 means no...
disability and no signs of impairment in any functional system and 3 means unimpaired walking, but either moderate disability in 1 functional system or mild disability in 3 or 4 functional systems). CARE-MS II included patients with an EDSS score between 0 and 5 (in which 5 means disability severe enough to impair normal daily activities and the person's ability to work a full day without special provisions, but they are still able to walk for 200 metres without aid or rest). All patients in CARE-MS II had to have previously received disease-modifying treatment with beta interferon or glatiramer acetate for 6 months in the preceding 10 years (the inclusion criteria also specified that more than 1 multiple sclerosis relapse had to have occurred while receiving these treatments), whereas patients in CARE-MS I and CAMMS223 did not.

3.3 The co-primary outcomes of the 3 trials were time to the onset of sustained accumulation of disability (specified as lasting for 6 months for CARE-MS I and CARE-MS II) and relapse rate. In the trials, patients were assessed quarterly using the EDSS to determine disability, and were assessed as needed for suspected relapses. Sustained accumulation of disability was defined as an increase lasting for 6 months of at least 1.5 points for people with a baseline EDSS score of 0, or 1.0 point for people with a baseline EDSS score of 1.0 or more. A relapse was defined as new or worsening neurological symptoms attributable to relapsing–remitting multiple sclerosis, lasting at least 48 hours, without fever, after at least 30 days of clinical stability, with an objective change on neurological examination. Data from CAMMS223 were analysed by intention to treat, and adjusted for country and baseline EDSS score, as prespecified in the statistical plan. In CARE-MS I and CARE-MS II only patients who had received at least 1 dose of trial medication were included in the analysis (that is, a modified intention-to-treat analysis). In CARE-MS II the analysis was also limited to patients who had followed the trial protocol (excluding patients who had not met all inclusion criteria). The results were adjusted for region.

3.4 In CARE-MS I 8% of people in the alemtuzumab treatment group had disability lasting for 6 months, compared with 11.1% in the Rebif group. There was no statistically significant difference in the rates of disability lasting for 6 months between people taking alemtuzumab and people taking Rebif (hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.4 to 1.23; p=0.22). In CARE-MS II 12.7% of people in the alemtuzumab treatment group had disability lasting for 6 months, compared with 21.1% in the Rebif group. This corresponded to a
statistically significant improvement of 42% with alemtuzumab (HR 0.58, 95% CI 0.38 to 0.87; \( p=0.008 \)). In CAMMS223 alemtuzumab statistically significantly reduced the risk of sustained accumulation of disability lasting for 6 months by 75% compared with Rebif (HR 0.25, 95% CI 0.11 to 0.57; \( p<0.001 \)). A separate extended follow-up study of CAMMS223 showed that over 5 years, alemtuzumab statistically significantly reduced the risk of sustained accumulation of disability lasting for at least 6 months by 69% compared with Rebif (HR 0.31, 95% CI 0.16 to 0.60; \( p=0.0005 \)).

3.5 Alemtuzumab statistically significantly reduced the relapse rate compared with Rebif: by 54.9% in CARE-MS I (RR [rate ratio] 0.45, 95% CI 0.32 to 0.63, \( p<0.0001 \)), by 49.4% in CARE-MS II (RR 0.51, 95% CI 0.39 to 0.65, \( p<0.0001 \)) and by 69% in CAMMS223 (RR 0.31, 95% CI 0.18 to 0.52, \( p<0.001 \)). The extended follow-up study of CAMMS223 showed that, over 5 years, alemtuzumab statistically significantly lowered the rate of relapse by 66% compared with Rebif (RR 0.34, 95% CI 0.20 to 0.57, \( p<0.0001 \)).

3.6 The manufacturer presented data from CARE-MS II and CAMMS223 (and its separate study extension) to compare alemtuzumab with Rebif in a subgroup of people with rapidly evolving severe relapsing–remitting multiple sclerosis (size of subpopulation not available). The manufacturer pooled the results of the 12-mg and 24-mg alemtuzumab arms of CAMMS223 because it considered that the results in each arm were sufficiently similar to allow this. The manufacturer stated that the analyses showed that the effectiveness of alemtuzumab compared with Rebif in the rapidly evolving severe relapsing–remitting multiple sclerosis subgroup was comparable to or greater than that seen in the overall trial populations. The reduction of risk in sustained accumulation of disability lasting at least 6 months was 51% in CARE-MS II (no \( p \) value reported) and 65% (\( p=0.036 \)) in the pooled group of CAMMS223. The analysis also indicated a statistically significant reduction in relapse rates for alemtuzumab compared with Rebif, of 56% (\( p=0.0018 \)) in the rapidly evolving severe relapsing–remitting multiple sclerosis subgroup of CARE-MS II and of 81% (\( p<0.0001 \)) in the pooled dose group of CAMMS223.

3.7 The manufacturer presented a mixed treatment comparison that compared alemtuzumab with each of the treatments in the decision problem (Rebif, intramuscular interferon beta-1a [Avonex], interferon beta-1b [Betaferon], glatiramer acetate, natalizumab and fingolimod). The manufacturer included 30
clinical trials identified in the systematic literature review, all of which recruited patients from the year 2000 onwards, and in which at least 80% of the patients had relapsing–remitting multiple sclerosis (the ‘base-case mixed treatment comparison’). The manufacturer justified the year 2000 as an appropriate cut-off point because annualised relapse rates have fallen in recent years and because the diagnostic criteria used in multiple sclerosis trials have changed. The manufacturer provided a separate ‘all years’ analysis that, in addition, included trials recruiting patients before the year 2000. The outcomes in the base-case mixed treatment comparison were annualised relapse rate, proportion of patients who were relapse free, sustained accumulation of disability lasting for 3 months, sustained accumulation of disability lasting for 6 months, discontinuation of treatment rate and discontinuation of treatment rate because of adverse events. In the base-case mixed treatment comparison, alemtuzumab led to statistically significantly lower annualised relapse rates than the beta interferons and glatiramer acetate. For the 3-month sustained accumulation of disability outcome, alemtuzumab was statistically significantly lower than Avonex, Betaferon and Rebif (44 micrograms); however, the difference between alemtuzumab and glatiramer acetate was not statistically significant. For the 6-month sustained accumulation of disability outcome, alemtuzumab was statistically significantly lower than Rebif (44 micrograms). While the point estimates for alemtuzumab compared with glatiramer acetate favoured alemtuzumab, the difference was not statistically significant. The results of the mixed treatment comparison were considered confidential by the manufacturer and therefore cannot be reported here.

3.8 The manufacturer carried out 2 separate mixed treatment comparisons of alemtuzumab for the subgroups of patients with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment (from CARE-MS II) and rapidly evolving severe relapsing-remitting multiple sclerosis (from CARE-MS I and II and CAMMS223). For the highly active relapsing-remitting multiple sclerosis despite beta interferon treatment subgroup, alemtuzumab had a lower annualised relapse rate than fingolimod; however, the difference was not statistically significant (HR 0.50, 95% CI 0.11 to 2.29). The 3-month sustained accumulation of disability was lower with alemtuzumab than with fingolimod but the difference was not statistically significant (HR 0.65, 95% CI 0.11 to 3.72). For the rapidly evolving severe relapsing-remitting multiple sclerosis subgroup, alemtuzumab had a lower annualised relapse rate than natalizumab; however, the difference was not statistically significant (HR 0.69,
95% CI 0.11 to 4.53). The 6-month sustained accumulation of disability was lower with alemtuzumab than with natalizumab, but the difference was not statistically significant (HR 0.78, 95% CI 0.06 to 10.83).

3.9 The manufacturer also presented a naïve indirect comparison of alemtuzumab compared with fingolimod and natalizumab for the subgroups of patients with highly active relapsing-remitting multiple sclerosis despite beta interferon therapy and patients with rapidly evolving severe relapsing-remitting multiple sclerosis respectively. The CARE MS-II study comparing alemtuzumab with active comparator (Rebif [44 micrograms]) showed that alemtuzumab had a greater treatment effect on 3-month sustained accumulation of disability in people with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment (HR 0.61, 95% CI 0.37 to 1.01) than fingolimod compared with placebo had in the FREEDOM study (HR 0.73, 95% CI 0.29 to 1.84). Studies comparing alemtuzumab with Rebif showed that alemtuzumab had a similar treatment effect on 6-month accumulation of disability in people with rapidly evolving severe relapsing-remitting multiple sclerosis (CAMMS223 [HR 0.3, 95% CI 0.13 to 0.69], CARE MS-I [HR 0.83, 95% CI 0.28 to 2.42] and CARE MS-II [HR 0.47, 95% CI 0.17 to 1.32]) to natalizumab compared with placebo in the AFFIRM study (HR 0.36, 95% CI 0.17 to 0.76).

3.10 In a pooled analysis of CARE-MS I, CARE-MS II and CAMMS223 results, most patients reported at least 1 adverse event, the majority of which were mild or moderate in severity. The most common adverse events were headache, rash, fever and multiple sclerosis relapse. The incidence of serious adverse events as reported at the end of the trials from the European Public Assessment Report (EPAR) was 18.3% in both the alemtuzumab and comparator arms. Independent investigators considered that the adverse events were related to alemtuzumab in 7.1% of all patients receiving 12 mg alemtuzumab and to Rebif in 1.6% of all patients receiving Rebif. The most frequently reported serious adverse events in the alemtuzumab 12 mg group were multiple sclerosis relapse (6.1%), pneumonia (0.4%), autoimmune thrombocytopenia (0.4%), gastroenteritis (0.4%), appendicitis (0.4%) and hives (0.4%). Four people developed idiopathic thrombocytopenic purpura. More thyroid-related adverse events were observed in the alemtuzumab arm of the trial (16.6%) than in the Rebif arm (5.2%). Thyroid-related adverse events were observed in 36.2% (at 4 years) and 44.7% (at 8 years) of patients in the alemtuzumab 12 mg/day group. The highest incidence of thyroid-related adverse events was observed between 24 and
42 months after the first treatment cycle. Other serious adverse events observed throughout the clinical trials included infections and renal disease. With the exception of thyroid disorders, administering more than 2 treatment cycles of alemtuzumab did not result in increased frequencies of common adverse events or clinically important events which had not already been observed. Eight people died during the clinical trials; 7 of these people had received alemtuzumab, and the EPAR states that the investigator judged that 3 deaths were possibly or likely to have been related to alemtuzumab treatment.

3.11 The manufacturer assessed health-related quality of life during the phase II and III trials using the Short-Form Health Survey (SF-36), the Functional Assessment of Multiple Sclerosis (FAMS) and the EuroQoL-5 Dimension-5 Level (EQ-5D-5L) questionnaire. In CARE-MS I and II, patients completed the SF-36 at baseline, at month 12, at month 24, and at early discontinuation of treatment. In CARE-MS I and II, the FAMS and EQ-5D-5L were assessed at baseline and every 6 months thereafter until month 24 or early discontinuation of treatment. In CAMMS223, patients completed the SF-36 every 6 months for 3 years, but not the FAMS or EQ-5D-5L. The manufacturer pooled the EQ-5D-5L utility scores from the CARE MS I and II trials in the alemtuzumab and Rebif (44 micrograms) arms at baseline and 24 months by EDSS score. The difference in mean utility values between patients with the same EDSS scores at baseline and at 24 months showed no consistent trend in either the alemtuzumab or the Rebif arms. The results were provided by the manufacturer as commercial in confidence.

Cost effectiveness

3.12 To assess the cost effectiveness of alemtuzumab the manufacturer submitted a multi-state Markov model reflecting the course of multiple sclerosis and the effect of treatment with alemtuzumab or the comparators defined in the decision problem (that is, Rebif, Avonex, Betaferon, glatiramer acetate, natalizumab and fingolimod). The model incorporated health states for the type of multiple sclerosis (relapsing–remitting or secondary progressive) and for disease severity defined by the level of disability (EDSS scores ranging from 0 [normal neurological examination] to 9 [confined to bed]). Patients with active relapsing–remitting multiple sclerosis entered the model at EDSS 0 up to EDSS 7 (an EDSS of 7 and above means patients have lost the ability to walk on their own). EDSS 10 represented death from multiple sclerosis. 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 multiple sclerosis, or died. The model assumed that when a patient progressed from relapsing–remitting multiple sclerosis to secondary progressive multiple sclerosis, their EDSS score increased by 1 point. The manufacturer chose a cycle length of 1 year, and a lifetime time horizon of 50 years. Patients entering the model had a mean age of 39.3 years, and there were approximately 3 times as many women as men. The analyses used an NHS and personal social services perspective and a 3.5% discount rate on costs and health effects. Most patients received only 2 courses of alemtuzumab, but the model included re-treatment for some patients in year 3, in years 6 to 9 and in year 10 or above (the manufacturer labelled the rates of re-treatment as commercial in confidence and so they cannot be presented here).

3.13 To estimate the rate of disease progression in people with relapsing–remitting multiple sclerosis, the manufacturer used a matrix to represent the natural history transition and disability progression in people who were not receiving disease-modifying therapies. The manufacturer chose the London Ontario dataset, a longitudinal observational study from 1989, to populate the natural history transition matrix. Since no data for patients with an EDSS state of 0 were available in this dataset, the manufacturer obtained transition probabilities for an EDSS 0 from the placebo arms of 2 trials (TOWER and TEMSO) that compared teriflunomide with placebo for treating multiple sclerosis. The manufacturer based the population entering the model on the average demographic profile of patients in the UK Risk Sharing Scheme, in which 85.8% have relapsing–remitting multiple sclerosis, the mean EDSS of patients with relapsing–remitting multiple sclerosis is 3.1, and the mean EDSS of patients with secondary progressive multiple sclerosis is 5.5.

3.14 To model the effect of treatment with alemtuzumab on relapsing–remitting multiple sclerosis, the manufacturer applied the hazard ratios for the outcome of disability sustained for 3 months compared with placebo from the base-case mixed treatment comparison (see section 3.7) to the natural history matrix. Separately, the manufacturer considered treatment effects on relapse rate and severity (whether or not the relapse leads to hospitalisation). In the base case, the manufacturer assumed that patients discontinue treatment when they convert from relapsing–remitting multiple sclerosis to secondary progressive multiple sclerosis, or progress to EDSS 7. After discontinuing treatment, patients were assumed to receive best supportive care only. The manufacturer's
model assumed that no patient who received alemtuzumab ever discontinued treatment, while patients could discontinue comparator treatments (and subsequently receive best supportive care). The manufacturer also assumed that the treatment effect of alemtuzumab did not change over time (even during years when patients did not receive alemtuzumab) until a patient reached EDSS 7 or converted to secondary progressive multiple sclerosis. On entering EDSS 7 the benefits of alemtuzumab stopped, independent of the number of courses of alemtuzumab given. In each cycle patients could stop using comparator treatments, discontinue treatment after reaching EDSS 7, or experience relapse or adverse events. The probability of death was dependent on the EDSS state (the higher the EDSS score, the higher the risk of death), age and sex.

3.15 The manufacturer's model applied health state utility values to each of the EDSS states. Although the manufacturer collected EQ-5D data in the CARE-MS I and II trials, it did not use these data in the model as they were not available at the time of submission. Instead, the manufacturer obtained health state utility values from Orme et al. (2007), a UK survey of health-related quality of life in (EQ-5D) in people with multiple sclerosis. Utility values decreased as EDSS scores increased, with the exception of the utility value for EDSS state 3, which was lower than EDSS 4. EDSS states 8 and 9 had negative utility values, indicating states that are considered to be worse than being dead. The manufacturer applied disutilities for a relapse, to caregivers, and for adverse events. The manufacturer obtained the value for the disutility of relapse from Orme et al. (2007), and the value for the disutility of relapse leading to hospitalisation from a US study (Prosser et al. 2003). To estimate disutility to caregivers, the manufacturer used values taken from Gani et al. (2008), and to estimate the time spent caring for the patient, the manufacturer used Orme et al. (2007). Disutility values applied for each adverse event were annualised based on the published literature. The manufacturer also took into account how long each adverse event lasted, and whether it was specific to treatment. The adverse events included infusion-associated reactions, bronchitis, herpes zoster, urinary tract infections, autoimmune thyroid-related adverse events, nephropathies, idiopathic thrombocytopenic purpura, other cytopenias and vomiting.

3.16 The model used NHS reference costs and the payment-by-results tariff to estimate the costs of administration, monitoring and adverse events associated with each treatment. The manufacturer assumed that monitoring of patients
previously treated with alemtuzumab lasts for up to 12 years. The manufacturer derived some costs from the literature: health state costs (including direct medical costs and direct non-medical costs) from a UK study (Tyas et al. 2007), and the costs associated with relapse from a study from the Republic of Ireland (Dee et al. 2012). For a sensitivity analysis, the manufacturer used an alternative UK study (Karampampa et al. 2012) to derive health state costs, although the manufacturer provided only natural history costs aggregated for EDSS states 0–3, 4–6 and 7–9, rather than costs for individual EDSS states. The manufacturer validated the resource use and costs it applied in the model using clinical experts. The cost of one of the comparators, fingolimod, includes a simple discount patient access scheme agreed with the Department of Health. However, the manufacturer did not know how large the discount was, and therefore could not use it in its base-case analysis. Instead, the manufacturer explored different prices of fingolimod in sensitivity analyses, using a range of assumed discounts.

3.17 The manufacturer’s submission presented the total life years gained, the total quality-adjusted life years (QALYs) and the total costs resulting from the economic model for alemtuzumab and Rebif (44 micrograms). Treatment with alemtuzumab was associated with 18.62 life years, which equated to 4.03 QALYs, at a total cost of £499,347. Treatment with Rebif (44 micrograms) was associated with 18.38 life years, which equated to 2.85 QALYs, at a total cost of £489,354.

3.18 The manufacturer conducted a fully incremental analysis, calculating the incremental QALY gains and costs for all treatment options and ordered by increasing costs. The treatments included alemtuzumab, glatiramer acetate, Rebif (22 micrograms), Rebif (44 micrograms), Avonex, and Betaferon. The manufacturer also included fingolimod and natalizumab in its incremental analysis, although it acknowledged that these drugs have marketing authorisations only for use in highly active relapsing-remitting multiple sclerosis despite beta interferon treatment and rapidly evolving severe relapsing–remitting multiple sclerosis. When compared in this incremental analysis, the probabilistic estimates of the incremental cost-effectiveness ratios (ICERs) suggested that:

- alemtuzumab dominated Betaferon, fingolimod (without applying a patient access scheme discount), fingolimod (assuming a patient access scheme price of £13,000 per
Rebif (44 micrograms) and Rebif (22 micrograms) were extendedly dominated by alemtuzumab. (A treatment is extendedly dominated when its ICER is higher than that of the next, more effective, option when compared with a common baseline.)

- The ICER for alemtuzumab compared with glatiramer acetate was £7017 per QALY gained. The manufacturer's deterministic results were similar with an ICER of £8924 per QALY gained for alemtuzumab compared with glatiramer acetate.

3.19 Using the results of the subgroup mixed treatment comparisons (see section 3.8), the manufacturer compared alemtuzumab with fingolimod and with natalizumab for the highly active relapsing-remitting multiple sclerosis despite beta interferon treatment and the rapidly evolving severe relapsing-remitting multiple sclerosis subgroups, respectively. For both analyses, alemtuzumab dominated the respective comparator.

3.20 The manufacturer conducted one-way sensitivity analyses, which showed that the cost effectiveness of alemtuzumab was most sensitive to the hazard ratios reflecting the comparative effectiveness of alemtuzumab compared with placebo for sustained disability progression, disease costs, and the discontinuation rate of Rebif (44 micrograms). Alemtuzumab continued to dominate all comparators except glatiramer acetate, except when the manufacturer varied the hazard ratios for disability progression. When the manufacturer applied the upper limit of the 95% confidence interval around the sustained accumulation of disability hazard ratio for alemtuzumab from the manufacturer's mixed treatment comparison, the resulting ICER for alemtuzumab compared with Rebif (44 micrograms) was £1,200,973 per QALY gained. With the lower limit of the 95% confidence interval, alemtuzumab dominated Rebif (that is, had the lowest total treatment costs for the greatest clinical gain of all treatments in the analysis).

3.21 The manufacturer also tested how sensitive the results were to which mixed treatment comparison it used, by using the 'all years' data instead of the 'base-case' mixed treatment comparison and by only including trials in which 100% of patients had relapsing–remitting multiple sclerosis (rather than the base-case mixed treatment comparison, in which trials with at least 80% of patients with relapsing–remitting multiple sclerosis were included). When trials from 'all
years’ in which at least 80% of patients had relapsing–remitting multiple sclerosis were included, the deterministic ICER for alemtuzumab compared with glatiramer acetate increased from £8924 to £9982 per QALY gained. When the manufacturer included trials from all years in which the percentage of the population with relapsing–remitting multiple sclerosis was 100% the ICER for alemtuzumab compared with glatiramer acetate increased to £27,434 per QALY gained. When the manufacturer used the mixed treatment comparison including trials after the year 2000 in which 100% of patients had relapsing–remitting multiple sclerosis, the ICER for alemtuzumab compared with glatiramer acetate was £10,822 per QALY gained.

3.22 The manufacturer conducted a number of scenario analyses using Rebif (44 micrograms) as the comparator, but not glatiramer acetate, with the justification that Rebif (44 micrograms) was the standard treatment for active relapsing–remitting multiple sclerosis. In the best case scenario alemtuzumab dominated Rebif and in the worst case scenario the ICER for alemtuzumab compared with Rebif was £20,388 per QALY gained. The manufacturer developed other scenarios based on:

- sourcing the baseline characteristics from the CARE-MS trials rather than from the UK Risk Sharing Scheme (the ICER for alemtuzumab compared with Rebif was £869 per QALY gained)

- using costs related to the natural history of multiple sclerosis from Karampampa et al. (2012) rather than Tyas et al. (2007) (alemtuzumab dominated Rebif)

- using natural history transition probabilities assuming that the population only included people with active relapsing–remitting multiple sclerosis, instead of all people with relapsing–remitting multiple sclerosis (the ICER for alemtuzumab compared with Rebif was £8597 per QALY gained)

- assuming long-term waning of treatment effect by 25% or 50% after year 5 for all treatments, instead of assuming that the beneficial effect of alemtuzumab does not wane (the ICERs for alemtuzumab compared with Rebif were £13,956 and £20,388 per QALY gained, respectively)

- assuming that treatment with alemtuzumab does not influence the probability of relapses or hospitalisation (the ICER for alemtuzumab compared with Rebif was £14,517 per QALY gained)
• using the trial data (pooled CARE-MS I and CARE-MS II) for the transition probabilities instead of using values sourced from the literature (alemtuzumab dominated Rebif).

**Evidence Review Group comments**

3.23 The ERG reviewed the manufacturer’s model and economic systematic review. The ERG commented that the structure of the economic model was appropriate for multiple sclerosis and consistent with previous economic evaluations of treatments for multiple sclerosis, and that the methods of analysis were appropriate and conformed to NICE methodological guidelines.

3.24 The ERG stated that the manufacturer systematically reviewed the literature to populate its transition matrix and reflect the natural history for disability progression for patients not receiving a disease-modifying treatment. The ERG did not find any data more appropriate than the London Ontario data identified by the manufacturer, but commented that the manufacturer did not fully explore the uncertainty around the natural history of multiple sclerosis. In light of previous technology appraisals, the ERG suggested that it would have been more appropriate to explore alternative sources of data.

3.25 The ERG evaluated the results of the economic model outputs as compared with published literature. The ERG noted that the manufacturer compared the results at the end of year 2, but no further. As there was no validation beyond 2 years, uncertainty remains as to the validity of longer-term outcomes.

3.26 The ERG stated that the manufacturer had performed appropriate structural sensitivity analyses, but had not conducted a sensitivity analysis that varied the rate of disease progression for patients receiving best supportive care only, or the rate of progression from relapsing–remitting multiple sclerosis to secondary progressive multiple sclerosis.

3.27 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 trial populations introduced uncertainty into the model, because these populations did not have the same baseline characteristics, particularly with regard to the distribution of initial EDSS states. The ERG commented that the conversion rate used for patients moving from relapsing–remitting multiple sclerosis to secondary progressive multiple sclerosis in the model was too high, because it did not reflect the people...
receiving first-line treatment for relapsing–remitting multiple sclerosis. The ERG also stated that the London Ontario estimates for disease progression for patients not taking disease-modifying treatments did not allow EDSS scores to improve. Trial-based transition probabilities were available that allowed EDSS scores to improve, although the ERG commented that using the trial data could pose problems as it reflected a short period of time. The ERG explored the impact of changing these assumptions in their exploratory analyses.

**Exploratory sensitivity analyses undertaken by the Evidence Review Group**

3.28 The ERG presented a 'preferred' base case that included alternative characteristics for the patient population, and a different progression rate from relapsing–remitting multiple sclerosis to secondary progressive multiple sclerosis. The ERG also conducted a series of sensitivity analyses to test uncertainties.

3.29 In all its exploratory analyses, the ERG compared alemtuzumab with Rebif (44 micrograms) (instead of glatiramer acetate as used in the manufacturer's fully incremental analysis). The ERG made this change because Rebif (44 micrograms) was the direct comparator in the clinical trials and was the most efficacious comparator in the manufacturer's mixed treatment comparison. Using the baseline characteristics for the populations in CARE-MS I and CARE-MS II, the ERG calculated that the ICER for alemtuzumab compared with Rebif (44 micrograms) would decrease from £8445 (manufacturer's base case comparing alemtuzumab with Rebif (44 micrograms) to £2869 per QALY gained. The ERG also applied a conversion rate of 15 years from relapsing–remitting multiple sclerosis to secondary progressive multiple sclerosis (instead of the 10–11 years used by the manufacturer), as used in Teriflunomide for treating active relapsing–remitting multiple sclerosis (NICE technology appraisal guidance 303). This had the effect of reducing the ICER to £3100 per QALY gained for alemtuzumab compared with Rebif (44 micrograms). The ERG's preferred approach combining these 2 changes resulted in alemtuzumab dominating (being less costly and more effective than) Rebif (44 micrograms), with a cost saving of £852 per QALY gained.

3.30 The ERG tested its preferred base case for alemtuzumab compared with Rebif (44 micrograms) in sensitivity analyses, including:
• reducing by 50% the transition probabilities to more severe health states from the London Ontario dataset (alemtuzumab dominated Rebif [44 micrograms])

• using quality-of-life utility values (upper and lower confidence intervals from the Orme et al. 2007 data used in the manufacturer’s model) (for both, alemtuzumab dominated Rebif [44 micrograms])

• using disease health state costs from Karampampa et al. (2012) and Biogen et al. (2007) (alemtuzumab dominated Rebif [44 micrograms] for Karampampa et al.; for Biogen et al., the ICER for alemtuzumab compared with Rebif [44 micrograms] was £4654 per QALY gained)

• reducing the cost of a relapse that results in hospitalisation from £6146 to £3039 (the ICER for alemtuzumab compared with Rebif [44 micrograms] was £1013 per QALY gained)

• applying a waning of treatment effect for alemtuzumab of 75% for year 10 and beyond, or 75% from year 6 to year 9 and 50% from year 10 and beyond (the ICERs for alemtuzumab compared with Rebif [44 micrograms] were £1815 and £7319 per QALY gained, respectively)

• varying the proportion of patients receiving additional alemtuzumab treatment at year 3 (60%) and years 5 and beyond (the ICER for alemtuzumab compared with Rebif [44 micrograms] was £8336 per QALY gained)

• applying the results from the 'all years' mixed treatment comparison (alemtuzumab dominated Rebif [44 micrograms])

• using the outcome of sustained accumulation of disability lasting for 6 months from the mixed treatment comparison (instead of 3 months) to calculate the disease transition probabilities (alemtuzumab dominated Rebif [44 micrograms]).

3.31 The ERG also explored the cost effectiveness of alemtuzumab for the treatment-naive and treatment-experienced subgroups separately, using the ERG preferred base case, the relative risk for annualised rate of relapse, and a sustained accumulation of disability lasting 3 months for alemtuzumab. Using the treatment-naive group data from CARE-MS I, the ERG’s preferred base case (that is, where alemtuzumab dominated Rebif [44 micrograms], see section 3.29) changed to an ICER of £6392 per QALY gained for alemtuzumab compared with Rebif (44 micrograms). When the ERG used the CAMMS223 data, alemtuzumab dominated Rebif (44 micrograms). Alemtuzumab also
dominated Rebif (44 micrograms) when the ERG pooled data from the 2 trials. For the treatment-experienced group, using effectiveness data from CARE-MS II, the ICER was £2854 per QALY gained for alemtuzumab compared with Rebif (44 micrograms).

3.32 The ERG also carried out exploratory analyses for the subgroup with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment, and the subgroup with rapidly evolving severe relapsing–remitting multiple sclerosis. In these analyses the ERG used its preferred base case for a slower progression to secondary progressive multiple sclerosis for the rapidly evolving severe relapsing–remitting multiple sclerosis subgroup, and different patient characteristics for the highly active relapsing-remitting multiple sclerosis despite beta interferon treatment subgroup. These changes had only minimal effect on the model results, and alemtuzumab continued to dominate fingolimod and natalizumab.

**Manufacturer's response to the appraisal consultation document**

3.33 The manufacturer provided a revised base case analysis using the Committee's preferred assumptions, as requested in the appraisal consultation document which did all of the following:

- used sustained accumulation of disability lasting 6 months as the primary outcome measure of the mixed treatment comparison
- used the 'all years' mixed treatment comparison adjusted for baseline relapse rates to estimate disease progression and withdrawal rates
- used the intention-to-treat analyses developed for the CAMMS223, CARE-MS I and CARE-MS II trials adjusted for baseline Expanded Disability Status Scale (EDSS) only (unadjusted for country or region)
- used the EQ-5D-5L utility scores pooled from the CARE MS I and II trials comparing alemtuzumab with Rebif (44 micrograms)
- used data on the natural history and progression of disability from the placebo arms of the TOWER and TEMSO trials to allow for improvements in patients' EDSS states
- incorporated the deaths observed in the trials into the model
assumed that the efficacy for alemtuzumab began waning at 3 or 5 years

• used additional costs of other licensed treatments for active relapsing–remitting multiple sclerosis after failure of alemtuzumab

• used a time-dependent rate of re-treatment for the costs of alemtuzumab

• removed the mid-cycle correction for the costs of alemtuzumab

• increased the number of monitoring and neurology visits for patients treated with alemtuzumab as well as visits for monitoring after restarting alemtuzumab treatment

• used the lower health state costs used in the ERG’s analyses

• used costs associated with adverse effects of treatment including renal failure, renal transplantation, dialysis and death

• used baseline characteristics from the alemtuzumab trials rather than from the UK Risk Sharing Scheme to populate the economic model.

The manufacturer applied the Committee’s preferences in individual analyses (see section 3.34) and also combined them into one analysis (see section 3.35).

3.34 In the manufacturer’s individual analyses using the baseline characteristics of patients in the alemtuzumab trials in the model instead of the UK Risk Sharing Scheme, alemtuzumab dominated glatiramer acetate. For each of the other individual analyses, the resulting probabilistic ICERs for alemtuzumab compared with glatiramer acetate remained below £20,000 per QALY gained with the exception of the analyses exploring the impact of waning effectiveness of alemtuzumab and its comparators. For these analyses, the manufacturer presented 2 scenarios; the first assumed a decreasing efficacy for both alemtuzumab and the comparators over time, and the second assumed decreasing efficacy only for alemtuzumab. When the manufacturer assumed that the treatment effectiveness for both alemtuzumab and its comparators was reduced from 100% to 75% from year 3 to year 5 after treatment, and then to 50% from year 6 onward, the manufacturer’s incremental analyses showed that glatiramer acetate dominated Avonex, Betaferon and Rebif (44 micrograms) and that the ICER for alemtuzumab compared with glatiramer acetate was £23,432 per QALY gained. When the manufacturer assumed that the effectiveness of alemtuzumab was reduced from 100% to 75% from year 3 to year 5, followed by a reduction to 50% from year 6 onward (while the efficacy of alemtuzumab’s
comparators remained unchanged) glatiramer acetate dominated Avonex, Betaferon and Rebif (44 micrograms) and the ICER for alemtuzumab compared with glatiramer acetate was £30,657 per QALY gained.

3.35 The manufacturer presented a fully incremental analysis combining each of the Committee's preferred assumptions including the 2 scenarios in which the effectiveness of treatments wanes over time. When the manufacturer assumed that the effectiveness for both alemtuzumab and its comparators was reduced from 100% to 75% from year 3 to year 5, followed by a reduction to 50% efficacy from year 6 onward, the manufacturer's incremental analyses showed that glatiramer acetate dominated Avonex, Betaferon and Rebif (44 micrograms) and that the ICER for alemtuzumab compared with glatiramer acetate was £13,636 per QALY gained. When the manufacturer assumed that the treatment effectiveness for alemtuzumab was reduced from 100% to 75% from year 3 to year 5, followed by a reduction to 50% efficacy from year 6 onward (while the efficacy of its comparators remained unchanged at 100%) glatiramer dominated Avonex, Betaferon and Rebif (44 micrograms) and the ICER for alemtuzumab compared with glatiramer acetate was £24,472 per QALY gained.

3.36 For the subgroup of rapidly evolving severe relapsing–remitting multiple sclerosis, when comparing alemtuzumab with natalizumab, the manufacturer used the Committee's preferred assumptions (see section 3.33) with the exception of using the results of the 'all years' mixed treatment comparison adjusted for baseline relapse rate because the manufacturer had not identified a relapse rate for natalizumab. When the manufacturer applied the Committee's assumptions individually, alemtuzumab dominated natalizumab for all but 1 scenario. In that scenario, the manufacturer assumed that the treatment effect for alemtuzumab waned beyond 3 years after treatment with alemtuzumab, while assuming that the treatment effect for natalizumab remained constant over the lifetime of the model. The ICER for this scenario was £236,172 per QALY gained. When the manufacturer combined all the Committee's preferred assumptions, alemtuzumab dominated natalizumab in the subgroup of people with rapidly evolving severe relapsing–remitting multiple sclerosis.

3.37 For the subgroup of patients with relapsing–remitting multiple sclerosis with high disease activity despite beta interferon treatment, when comparing alemtuzumab with fingolimod, the manufacturer used the Committee's
preferred assumptions (see section 3.33) with the exception of 2 assumptions for which the manufacturer did not identify data. These 2 assumptions were sustained accumulation of disability lasting 6 months as a primary outcome measure in the mixed treatment comparison, and using the results of the ‘all years’ mixed treatment comparison adjusted for baseline relapse rate. When the manufacturer applied the Committee’s assumptions individually, alemtuzumab dominated fingolimod in all scenarios. When the manufacturer combined all the Committee’s assumptions, alemtuzumab continued to dominate fingolimod.

3.38 For the same subgroup, that is, patients with relapsing–remitting multiple sclerosis with high disease activity despite beta interferon treatment, and when comparing alemtuzumab with fingolimod, the manufacturer explored additional scenarios. The manufacturer combined all of the Committee’s preferred assumptions (see section 3.33) and:

- assumed that the hazard ratios from patients with relapsing–remitting multiple sclerosis with high disease activity despite beta interferon treatment in CARE MS II, which reflected the effectiveness of alemtuzumab compared with Rebif (44 micrograms) to delay disability (sustained accumulation of disability at 3 months) and annual relapse rates, were equivalent to what would have been expected had alemtuzumab been compared with placebo

- incorporated these assumptions together with the hazard ratios from the subgroup of patients with relapsing–remitting multiple sclerosis with high disease activity despite beta interferon treatment in the FREEDOMS trial which compared fingolimod with placebo

- assumed that the patient access scheme price for fingolimod (the details of which were not available to the manufacturer of alemtuzumab) was £13,000 and

- applied either the utility values from CARE-MS I and II or those from the placebo arms of the TEMSO study (teriflunomide versus placebo) combined with the utility values reflecting relapses from Orme et al.

The ICERs resulting from these analyses for alemtuzumab compared with fingolimod in patients with relapsing–remitting multiple sclerosis with high disease activity despite beta interferon treatment were £7,089 per QALY gained using the CARE-MS I and II trial utility results and £17,232 per QALY gained using the utility results from the placebo arms of the TEMSO study combined with the Orme study utility decrements.
Evidence Review Group comments on the manufacturer's additional evidence

3.39 The ERG confirmed that the additional evidence presented by the manufacturer reflected the Committee's requests for additional analyses. The ERG confirmed that it could calculate the manufacturer's deterministic ICERs both in the individual analyses and in the Committee's preferred combined analysis but, owing to time constraints, it could only verify a sample of the probabilistic results presented by the manufacturer. The ERG noted that the manufacturer had incorrectly estimated the ICERs in its fully incremental analyses because the manufacturer compared the treatment with the next less costly treatment, even when the next less costly treatment was dominated.

3.40 The ERG reviewed the manufacturer's response to the ACD which focused on both subgroups reflecting patients with high disease activity. The ERG noted that while the manufacturer's mixed treatment comparison provided evidence of the effectiveness of alemtuzumab in these subgroups, there remained a number of uncertainties with these data: the evidence network depended on the teriflunomide trials which included either the overall relapsing-remitting multiple sclerosis population (TENERE) or a subgroup of previously-treated patients as a proxy for highly active relapsing-remitting multiple sclerosis despite beta interferon treatment (TEMSO and TOWER); inconsistencies in the definitions of the subgroups in each of the trials; differences between the patient populations included in the trials; and that the mixed treatment comparison was heavily dependent on indirect evidence to complete the evidence network.

3.41 The ERG conducted exploratory analyses that assumed that alemtuzumab and fingolimod were equally effective, and that alemtuzumab and natalizumab were equally effective. To do this, the ERG applied the hazard ratios for annual relapse rates and sustained accumulation of disability from the mixed treatment comparison for alemtuzumab compared with placebo and fingolimod and natalizumab each compared with placebo. The ERG applied hazard ratios for alemtuzumab to fingolimod and natalizumab (and vice versa) in the respective subgroups, and also applied the midpoint hazard ratio between alemtuzumab and either fingolimod or natalizumab. In the subgroup of high disease activity despite beta interferon treatment when comparing alemtuzumab with fingolimod, the resulting ICERs were £4,460, £14,788 and £8,942 per QALY gained, respectively. In the subgroup of rapidly evolving severe
relapsing–remitting multiple sclerosis, alemtuzumab dominated natalizumab in each scenario.

3.42 Full details of all the evidence are in the manufacturer's original submission, the manufacturer's response to consultation, the ERG's original report, and the ERG's critique of the manufacturer's response to consultation.
4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of alemtuzumab, having considered evidence on the nature of active relapsing–remitting multiple sclerosis and the value placed on the benefits of alemtuzumab by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.2 The Committee heard from the clinical specialists and patient experts about the nature of the condition. It was aware that relapsing–remitting multiple sclerosis is a chronic, disabling, neurological condition that, as it progresses, is life altering and has a large negative impact on quality of life and activities of daily living. The Committee heard from clinical specialists that the currently available first-line treatments for active relapsing–remitting multiple sclerosis need to be injected weekly or several times per week and can be associated with unpleasant side effects (such as injection-site reactions, flu-like symptoms, fatigue and depression) and can significantly affect patients' emotional wellbeing. The Committee concluded that any delay in relapse and progression of disability or reduction in the frequency of treatment would have a positive impact on the lives of people with multiple sclerosis and their families.

4.3 The Committee considered the impact of treating active relapsing–remitting multiple sclerosis with alemtuzumab. The Committee was aware that patients in the UK may have participated in trials of alemtuzumab, or may have received alemtuzumab off-label before it was licensed for active relapsing–remitting multiple sclerosis (alemtuzumab had a previous marketing authorisation for B-cell chronic lymphocytic leukaemia, but the manufacturer has withdrawn the product for that indication). The Committee heard from a patient expert who received alemtuzumab for active relapsing–remitting multiple sclerosis in 2006 and 2007, and who has not experienced any relapses since, with her health being better now than at the time of diagnosis. She also preferred alemtuzumab's administration schedule (see section 2.1) to weekly or daily self-administered injections with beta interferons, which to her would have been a 'constant reminder' of her multiple sclerosis. She commented that the considerable impact on her family and their concern about relapse or accumulation of disability lessened once she had received alemtuzumab. The
Committee concluded that alemtuzumab has the potential to benefit people with active relapsing–remitting multiple sclerosis and their families.

4.4 The Committee considered alemtuzumab’s place in the treatment pathway for active relapsing–remitting multiple sclerosis. The Committee heard from the clinical specialists that alemtuzumab would be considered as a first-line treatment option, alongside beta interferons or glatiramer acetate, for people with active relapsing–remitting multiple sclerosis eligible for treatment under the Association for British Neurologists' guidelines. The Committee heard from the clinical specialists that, while effective therapies should ideally be offered early in disease, offering effective treatments later in disease is even more important because these patients have a higher risk for more severe complications. The Committee also heard that, while alemtuzumab's marketing authorisation permits its use as a first-line treatment, it is more likely to be offered to people for whom other disease-modifying treatments have not been effective. However, the Committee heard from the patient expert that a patient should not have to experience more severe symptoms before being offered alemtuzumab. One clinical specialist emphasised that alemtuzumab is 'not for everybody', and that clinicians would offer alemtuzumab to patients who, among other characteristics, would be likely to comply with the required monitoring for adverse effects, and that approaches exist to estimate the likely compliance with monitoring. The Committee concluded that alemtuzumab is a valuable treatment option for selected patients with varying types and stages of active relapsing–remitting multiple sclerosis.

4.5 The Committee considered whether neurologists would offer patients treatment with alemtuzumab beyond the 2 annual cycles stipulated in the marketing authorisation. The clinical specialists acknowledged that some patients need more than the 2 initial annual cycles, and that clinicians would consider offering further courses of alemtuzumab to patients whose disease had relapsed. One clinical specialist stated that people who have no relapses in the third year following first treatment, but who subsequently relapse, would be considered for retreatment. People who have relapses within the third year would not, however, be offered retreatment because clinicians would consider alemtuzumab to be no longer effective in this situation. The Committee concluded that some patients whose disease initially responds to alemtuzumab but later relapses may be treated with alemtuzumab beyond the 2 treatment courses described in the marketing authorisation.
The Committee considered the advantages and disadvantages of alemtuzumab treatment. The clinical specialists described advantages to alemtuzumab treatment, including that it is highly effective, does not cause the flu-like symptoms associated with beta interferons, and does not need to be discontinued by patients planning a pregnancy, although the Committee was aware that effective contraceptive measures should be taken when receiving alemtuzumab and for 4 months following a course of treatment according to the summary of product characteristics. This was seen as important, because multiple sclerosis affects women and men during the years when they are most likely to have children, and all other multiple sclerosis treatments, according to their summary of product characteristics, must be stopped for a person to have children. The clinical specialists explained that the main disadvantages of alemtuzumab treatment are the possible serious adverse effects observed during the trials, including idiopathic thrombocytopenic purpura, kidney disease or failure, thyroid disease and death. The clinical specialists stated that thyroid disease is the most common complication, affecting one-third of patients with multiple sclerosis treated with alemtuzumab. In response to a comment made by a consultee that patients treated with alemtuzumab were at risk for papillary thyroid cancer, a clinical specialist suggested that this could be related to increased detection following routine screening as required by the marketing authorisation for alemtuzumab. The clinical specialists and the manufacturer explained that patients need monthly platelet and white cell counts and quarterly assessment of thyroid and renal function for 4 years after the last treatment, and that patients are monitored even more often than this immediately after treatment with alemtuzumab. The clinical specialists stated that alemtuzumab permanently changes a person's immune system because it alters the numbers, proportions and properties of some lymphocyte subsets, and acknowledged that ongoing monthly monitoring might be an obstacle for some patients, particularly for those who feel well. The Committee expressed concern about the methods used to ensure that people treated with alemtuzumab would comply with monitoring requirements. The Committee heard from the clinical specialists that there are standard monitoring systems in place at the specialist centres that administer alemtuzumab and patients are contacted by a variety of methods if they miss a monthly monitoring visit. The Committee was aware that even when adverse events related to alemtuzumab were identified during regular monitoring, there could still be problems with follow-up actions when the results are received. The clinical specialists commented that idiopathic thrombocytopenic purpura associated with
Alemtuzumab responds to treatment with corticosteroids and immunoglobulin G, and patients would be unlikely to need treatment with thrombopoietin agonists. The clinical specialists and patient experts acknowledged the risk of renal disease for which some patients need renal replacement therapy but stated that people with active relapsing–remitting multiple sclerosis may be willing to accept the risks of serious adverse events associated with alemtuzumab treatment, because the potential benefits to quality of life are considerable. The clinical specialists acknowledged uncertainty about how prior treatment with alemtuzumab might change the adverse event profile of other monoclonal antibodies used for the treatment of multiple sclerosis, such as natalizumab. The Committee concluded that alemtuzumab is associated with significant benefits, but also significant harms, that some people with active relapsing–remitting multiple sclerosis are willing to accept the disadvantages of alemtuzumab treatment, and that adhering to the recommended monitoring schedule is important.

4.7 The Committee further considered the adverse effects associated with alemtuzumab. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency acknowledged that alemtuzumab had been shown to be effective in people with active relapsing–remitting multiple sclerosis, but that there were serious safety concerns evidenced by the fact that 7 CHMP members had publicly disagreed with the majority decision. These dissenting members stated in the European Public Assessment Report for alemtuzumab that the benefits to risks balance could be considered acceptable in a limited indication in patients with relapsing–remitting multiple sclerosis with high disease activity defined by clinical and imaging features, but that they did not consider that the benefits outweighed the risks in a population with less active disease. The Committee took into account the view of a clinical specialist that the deaths that occurred during the clinical trials could have been avoided. It concluded that a clinical trial provides better opportunities for regular monitoring than could be achieved in clinical practice, and remained concerned about the deaths that were possibly related to alemtuzumab treatment.

4.8 The Committee discussed the information provided to patients for whom treatment with alemtuzumab is considered, and specifically the requirements for monitoring and risks associated with treatment with alemtuzumab. The Committee questioned whether those requirements and risks were being clearly communicated to patients considering alemtuzumab as a treatment
option. The Committee heard from the clinical specialists that alemtuzumab would only be offered to people who were fully informed of the possible adverse effects of alemtuzumab and aware of the stringent monitoring requirements. The patient expert explained that she had been fully informed about the possible adverse effects and monitoring requirements for alemtuzumab before making the decision to enrol in the alemtuzumab trial and further information had been provided during the initial stages of treatment to help her recognise possible adverse reactions. The Committee was aware that the summary of product characteristics requires that a neurologist experienced in treating patients with multiple sclerosis supervises treatment with alemtuzumab, and states that specialists and equipment should be available to diagnose and manage the most frequent adverse reactions, especially autoimmune conditions and infections. The Committee was also aware that patients should be given a Patient Alert Card and Patient Guide and be informed about the risks of alemtuzumab. The Committee remained concerned that not all people offered alemtuzumab might understand the risks or comply with the monitoring requirements. The Committee concluded that there are monitoring processes in place based on evidence from patients who received alemtuzumab either in trial or clinical settings.

**Clinical effectiveness**

4.9 The Committee considered the clinical effectiveness of alemtuzumab in the relapsing–remitting multiple sclerosis population in the 3 trials comparing it with Rebif (44 micrograms) (see section 3.2). On the basis of the improvements in sustained accumulation of disability at 6 months in the trials and in relapse rates, the Committee concluded that alemtuzumab is a more clinically effective treatment for active relapsing–remitting multiple sclerosis than Rebif (44 micrograms).

4.10 The Committee discussed whether it was appropriate for the manufacturer to have used the sustained accumulation of disability lasting 3 months rather than 6 months in its mixed treatment comparison and modelling for people with active relapsing–remitting multiple sclerosis, given that the CARE-MS I and II trials included 6-month sustained accumulation of disability as one of the co-primary endpoints (the other being annualised relapse rate). The Committee heard from the clinical specialists that patients may not have permanent disability progression after a relapse and that recovery may take up to
12 months, but on average people will recover within 3 or 4 months. The clinical specialists stated that sustained disability progression lasting for 6 months is a more appropriate outcome measure than disability progression lasting for 3 months. The Committee heard from the manufacturer that the main reason for why it initially chose to use the sustained accumulation of disability at 3 months in its mixed treatment comparison was that this would allow for comparison across trials that included 3-month but not 6-month disability. However the Committee understood that the 6-month disability outcome was reported for all but 1 of the beta interferons. On the basis of clinicians' preference, the Committee concluded that it preferred sustained accumulation of disability lasting 6 months to be used as the primary outcome measure in the mixed treatment comparison.

4.11 The Committee discussed the manufacturer's mixed treatment comparison comparing alemtuzumab with other disease-modifying treatments for people with active relapsing–remitting multiple sclerosis. It noted that the manufacturer initially presented a base-case mixed treatment comparison excluding trials that recruited patients before the year 2000, and a separate 'all years' sensitivity analysis that included all trials (see section 3.7). The Committee acknowledged that earlier trials were excluded because of changes in diagnostic criteria, which resulted in part in changes in baseline relapse rates over time, but were concerned that important trials were excluded as a result of the cut-off date, including all trials comparing beta interferons with placebo. In addition, the Committee was not convinced that the difference in the baseline rate of relapse would modify the relative effectiveness of alemtuzumab compared with other disease-modifying drugs. It was aware that the manufacturer presented a revised mixed treatment comparison including trials from 'all years' and adjusted for baseline relapse in its response to the Appraisal Consultation Document. The Committee concluded that it is more appropriate for the mixed treatment comparison to include all available evidence, and that in this case adjusting the mixed treatment comparison for baseline relapse rates accounts for any differences in relapse rates between trials.

4.12 The Committee discussed the statistical analysis plan for the 3 alemtuzumab trials. The Committee noted that the statistical plan for CAMMS223 stipulated an intention-to-treat analysis adjusted for baseline Expanded Disability Status Scale (EDSS) score and country, which was reflected in the final publication. The Committee noted that in CAMMS223 and CARE-MS II, the investigators used
the per-protocol set to conduct the statistical analyses whereas in CARE-MS I the full dataset was analysed, which included some patients who did not meet the specified inclusion criteria or who had not received treatment as specified in the clinical trial protocol. The Committee heard from a clinical specialist, and author of all 3 trials, that the results for the full analysis set were similar to those for the per-protocol set for CARE-MS I. However, the Committee remained concerned about the pooling of trial results that had been analysed differently, and the fact that the manufacturer had not initially presented a sensitivity analysis demonstrating the impact this difference could have on the results of the mixed treatment comparison (and therefore on the economic modelling). The Committee concluded that it is more appropriate to include the per-protocol analyses set for all 3 trials, unadjusted for country or region and adjusted for baseline EDSS states only. However, it was aware that the manufacturer's revised mixed treatment comparison presented in its response to the appraisal consultation document included the results from intention-to-treat analyses of the CARE-MS I, CARE-MS II and CAMMS223 trials and concluded that in this case it had little impact on the results of the mixed treatment comparison.

4.13 The Committee considered the long-term efficacy of alemtuzumab. The clinical specialists acknowledged that there was uncertainty regarding the effectiveness of alemtuzumab in the long term and specifically for periods exceeding the duration of the follow-up studies to the clinical trials, which to date have followed some patients for a median of 7 years and a maximum of 12 years. The clinical specialists also stated that people who experience a relapse soon after treatment with alemtuzumab will probably be offered alternative treatment which, for severe disease, could include bone marrow transplantation. One clinical specialist noted that, in the trials, the number of people for whom alemtuzumab was no longer effective was small. The Committee concluded that, for some people, alemtuzumab might not provide long-term enduring effect and other treatments might be required.

4.14 The Committee considered the clinical effectiveness of alemtuzumab in people with rapidly evolving severe relapsing-remitting multiple sclerosis or highly active relapsing-remitting multiple sclerosis despite beta interferon treatment, for which the relevant comparators would be natalizumab and fingolimod respectively. The Committee heard from a clinical specialist that alemtuzumab was probably more effective than fingolimod, and probably equally effective to
natalizumab. However, compared with natalizumab, alemtuzumab was probably safer in pregnancy and in people testing positive to John Cunningham virus, which can lead to progressive multifocal leukoencephalopathy. The Committee commented that the clinical effectiveness of alemtuzumab in the rapidly evolving severe relapsing-remitting multiple sclerosis or highly active relapsing-remitting multiple sclerosis despite beta interferon treatment subgroups was not robustly demonstrated. It was aware that no trials exist that directly compare alemtuzumab with either natalizumab or fingolimod. The Committee understood that the mixed treatment comparisons required a number of links to compare alemtuzumab with either natalizumab or fingolimod, and that different trials defined the subgroups differently, and both these factors increased uncertainty. The Committee noted that the results of the mixed treatment comparison had shown that alemtuzumab was associated with a lower annualised relapse rate and 3 month sustained accumulation of disability than fingolimod for the subgroup of highly active relapsing-remitting multiple sclerosis despite beta interferon treatment, although these differences were not statistically significant. The Committee also noted that alemtuzumab treatment led to lower annualised relapse rates and lower 6-month sustained accumulation of disability than natalizumab for the subgroup of rapidly evolving severe relapsing-remitting multiple sclerosis, although the difference was not statistically significant. The Committee noted that the CARE MS-II study comparing alemtuzumab with Rebi (44 micrograms) showed that alemtuzumab had a greater absolute treatment effect on 3-month sustained accumulation of disability in people with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment than that of fingolimod compared with placebo in the FREEDOM study. The Committee also noted that in the CAMMS223, CARE MS-I and II studies (that compared alemtuzumab with Rebi [44 micrograms]) alemtuzumab had a similar effect on 6-month sustained accumulation of disability in people with rapidly evolving severe relapsing-remitting multiple sclerosis to that of natalizumab compared with placebo in the AFFIRM study. Acknowledging the uncertainty, the Committee was persuaded that alemtuzumab was at least as effective as fingolimod and natalizumab for people with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment and rapidly evolving severe relapsing-remitting multiple sclerosis respectively.
Cost effectiveness

4.15 The Committee considered the QALYs accumulated over the course of the modelled time horizon, and the consequences of assuming that people can only move to worse EDSS states (that is, a person's condition can deteriorate or stay the same but not improve) regardless of treatment. The Committee noted that for the full time horizon, a person who received treatment with alemtuzumab would accrue just over 4 QALYs despite accruing 18 life years (see section 3.17). It further noted that the modelled life years for the comparator (Rebif [44 micrograms]) was also much higher than the corresponding number of modelled QALYs. The Committee considered this to be an implausibly low number of QALYs to be accrued by a person with multiple sclerosis over the course of their lifetime. It therefore reasoned that that the original economic model had poor face validity. The manufacturer could not explain the low total lifetime QALY values estimated within the model nor did it explore what might have caused the model to do this. The ERG commented that it was probably because the manufacturer had used the London Ontario data to define the natural history of disease in the absence of disease-modifying therapies, which only allowed a person to progress towards further disability on the EDSS. The Committee heard that the alemtuzumab trial data and other evidence provided by the patient expert and the clinical specialists suggested that people's EDSS states could improve. The Committee was aware that this would considerably affect the number of QALYs accrued by a modelled patient population over a lifetime. The Committee noted that EDSS states of 8 and above were associated with negative utility values, which would reduce lifetime QALYs accrued. The Committee commented that discounting alone was unlikely to explain the low number of lifetime QALYs accrued in the original economic model. The Committee concluded that it is appropriate for the economic modelling to allow patients with relapsing–remitting multiple sclerosis to move to lower as well as to higher EDSS states (that is, to allow for the condition to either improve or get worse) which is in line with what is seen in clinical practice for the lower EDSS states.

4.16 The Committee considered the health-related quality of life data used in the model. The Committee considered that the trials would provide the most appropriate source of quality of life data for the analysis, because the trial population best reflects the population that would receive the treatment if it were available in clinical practice. The Committee was concerned about the
manufacturer’s initial choice of values to reflect the disutility associated with some of the adverse effects. The clinical specialists agreed that, for example, it is not plausible that a patient with leukocytopenia would have no disutility. The Committee was also aware that a number of deaths were observed in the trials (see section 4.7) and noted that this needed to be reflected in the economic modelling. The Committee understood that in its response to the appraisal consultation document, the manufacturer had pooled EQ-5D-5L utility scores by EDSS state from CARE-MS I and CARE-MS II both at baseline and after 24 months of treatment and had accounted for the deaths observed in the trials in its economic modelling. The manufacturer explained that the difference in mean utility values between baseline and at 24 months in patients with the same EDSS scores did not show improved utility, as might have been expected. The Committee concluded that it is appropriate for the economic modelling to include the deaths observed in the trials and also the trial EQ-5D-5L data (which is more likely to capture the disutility of adverse events associated with alemtuzumab than the manufacturer’s original approximations).

The Committee considered the manufacturer’s assumption that the treatment effect from alemtuzumab would persist for many years after the last treatment. The Committee questioned whether a constant treatment effect was biologically plausible. In response, a clinical specialist stated that alemtuzumab permanently modifies a person’s immune system, which may be why alemtuzumab’s treatment effect might be life-long. However, the clinical specialist stated that there were no data comparing immune markers in people whose disease does and does not progress after treatment with alemtuzumab. The clinical specialists also commented that the long-term benefit of alemtuzumab is unknown given the absence of long-term data, but that it would be reasonable to assume that alemtuzumab’s treatment effect might start to decrease between 3 and 5 years after treatment but that this, too, was uncertain. The Committee concluded that the manufacturer’s initial assumption of constant treatment effect throughout the course of a person’s multiple sclerosis up to EDSS state 7 or secondary progressive multiple sclerosis was not supported by data, and that the clinical specialists had suggested a maximum of 5 years before waning occurs. The Committee concluded that because of the uncertainty about the long-term treatment effect from alemtuzumab it is appropriate to incorporate a 3- and 5-year waning effect into the model, and it was satisfied that the manufacturer’s revised economic analyses adequately
explored the sensitivity of the ICER to several scenarios which assumed that the
effectiveness of alemtuzumab and its comparators waned over time.

4.18 The Committee discussed re-treatment with alemtuzumab. It was aware from clinical specialists that, in CARE-MS I, CARE-MS II and CAMMS233, a further cycle of alemtuzumab was offered to patients if a relapse that lasted for at least 24 hours occurred after the second annual course of infusions. It also heard from clinical specialists that further treatments were considered likely in UK clinical practice. The Committee heard from the clinical specialists that, in the trials, the percentage of people who needed a third course was greater than the percentage who needed a fourth course, and that the trend of fewer people needing successive courses lasted up to 7 years (the median follow-up time for which data were available). The Committee considered that this indicated a time-dependent rate of re-treatment. The Committee concluded that it is appropriate to incorporate the time-dependent rate of re-treatment from the trials in the model and was satisfied that in its response to the Appraisal Consultation Document, the manufacturer had reflected this in its revised economic model.

4.19 The Committee considered the costs included in the economic model for alemtuzumab. The Committee noted that the manufacturer’s original economic model included a mid-cycle correction, although alemtuzumab is given at the start of the cycle. The Committee was also concerned that the number of visits to neurologists included in the manufacturer’s original economic model for people receiving alemtuzumab was low. Although the ERG increased the number of visits to neurologists (and the additional related costs) to 4 in year 1 and 2 in subsequent years, it did not take into account that people receiving 3 or more courses of alemtuzumab treatment would need 4 visits in the first year of restarting treatment. The Committee noted from the ERG exploratory analyses that using alternative health states costs had a large impact on the cost effectiveness of alemtuzumab (see section 3.30). The Committee commented that it would have been more appropriate for the manufacturer to incorporate the health state costs used by the ERG in their exploratory analyses (that only included direct ‘medical’ costs rather than both ‘medical’ and ‘non-medical’ costs) because this is more consistent with NICE’s preferred methods as presented in its Guide to the methods of technology appraisal. It noted that the manufacturer did not initially include the costs associated with adverse effects of treatment including renal failure, renal transplantation, dialysis and death.
The Committee concluded that it was satisfied that the manufacturer's revised analyses adequately addressed and explored all of these uncertainties associated with the costs included in the economic model.

4.20 The Committee discussed the data sources chosen by the manufacturer to reflect the baseline characteristics of patients with relapsing–remitting multiple sclerosis and the natural history of disease progression for patients not taking disease-modifying therapies. The Committee agreed that it was more appropriate for the manufacturer to use trial data to determine the initial EDSS distribution because this was representative of the patient population likely to be treated with alemtuzumab in the UK. The Committee was aware that the manufacturer of alemtuzumab also manufactures teriflunomide and has collected data in the TOWER and TEMSO trials, both of which include groups of patients randomised to placebo. It concluded that this dataset would more accurately reflect the natural history of disease (underlying progression without disease-modifying therapy) in people who would be treated with alemtuzumab in the UK. It concluded that it is appropriate to incorporate the baseline characteristics of patients in the alemtuzumab trials instead of using data from the UK Risk Sharing Scheme, and that it is appropriate to incorporate the rates of disease progression in the placebo group from the TOWER and TEMSO trials to reflect the natural history of the disease.

4.21 The Committee considered the manufacturer's revised base-case results submitted in response to consultation (see section 3.35). It was aware that for the active relapsing–remitting multiple sclerosis population, the manufacturer had incorporated all the Committee's preferred assumptions (see sections 3.33, 4.10–4.12 and 4.15–4.20). The Committee noted that when assuming that the effect of treatment decreased for alemtuzumab and not for the comparators, the ICER for alemtuzumab compared with glatiramer acetate was £24,500 per QALY gained and that if the model assumed that the effectiveness of both alemtuzumab and its comparators waned, the ICER for alemtuzumab compared with glatiramer acetate was £13,600 per QALY gained. The Committee concluded that alemtuzumab could be considered a cost-effective use of NHS resources for treating adults with active relapsing–remitting multiple sclerosis.

4.22 The Committee also considered the manufacturer’s revised analyses for the subgroups characterised by highly active relapsing–remitting multiple sclerosis despite beta interferon treatment and rapidly evolving severe relapsing-
remitting multiple sclerosis, submitted in response to consultation. The clinical specialists noted that the terms used to describe these subgroups of patients are not generally used in UK clinical practice. The Committee was aware that the manufacturer’s mixed treatment comparisons for these subgroups had not generated statistically significantly effects for alemtuzumab compared with the relevant comparator (see section 4.14) and was associated with uncertainty. The Committee heard during consultation from the Association of British Neurologists that it would be impractical to recommend ‘a potent drug with significant side effects for patients with modestly active disease but not patients whose future is most threatened by their disease’. The Committee also heard the clinical specialists confirm that it would be clinically counterintuitive to recommend alemtuzumab for the overall active relapsing–remitting multiple sclerosis population, but not recommend it for the highly active relapsing–remitting multiple sclerosis despite beta interferon treatment and the rapidly evolving severe relapsing-remitting multiple sclerosis subgroups for whom the need for treatment options was even greater. The Committee noted that the approach taken by the ERG assumed equal efficacy between alemtuzumab and fingolimod or natalizumab using a midpoint of the hazard ratios for treatment compared with placebo and applied it to the manufacturer’s revised economic model. It agreed that this was a pragmatic way to determine the relative clinical and cost effectiveness of alemtuzumab in these subgroups given the uncertainty. The Committee noted that the most plausible ICER for patients with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment was £8900 per QALY gained for alemtuzumab compared with fingolimod. The Committee noted that for patients with rapidly evolving severe relapsing-remitting multiple sclerosis, alemtuzumab dominated natalizumab (that is, less expensive and more effective). The Committee therefore concluded that alemtuzumab could be considered a cost-effective use of NHS resources for people with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment and for people with rapidly evolving severe relapsing-remitting multiple sclerosis.

4.23 The Committee considered the manufacturer’s assumptions about when people should receive disease-modifying therapies such as alemtuzumab and how this was incorporated into the manufacturer’s economic model. The Committee noted that only patients with active relapsing–remitting multiple sclerosis in an EDSS state of 0 to 7 entered the model and that treatment with alemtuzumab would stop when a patient progresses to EDSS 7 or upon secondary progressive
multiple sclerosis. It acknowledged that these assumptions were based on the Association of British Neurologists’ guideline for prescribing of disease modifying treatments in multiple sclerosis. The Committee agreed that the manufacturer presented an economic model that supported the use of alemtuzumab in people with active relapsing–remitting multiple sclerosis in an EDSS state less than 7.

4.24 The Committee discussed whether alemtuzumab can be considered an innovative treatment, providing a step change in the treatment of active relapsing–remitting multiple sclerosis and providing benefit not accounted for in the modelling. The Committee heard from the clinical specialists and patient expert that alemtuzumab has been a revolutionary treatment for some people, allowing them to live their lives as they had before being diagnosed with multiple sclerosis. The clinical specialists believed that it was a step change because it delayed disease progression. The Committee noted that alemtuzumab did provide a step change in the treatment of active relapsing–remitting multiple sclerosis. However, the Committee considered that these benefits would already be captured through increased efficacy gains, both in survival gains and in quality of life gains. The Committee therefore concluded that no additional QALY gains should be attributed to alemtuzumab to account for these benefits.

**Summary of Appraisal Committee’s key conclusions**

<table>
<thead>
<tr>
<th>TA312</th>
<th>Appraisal title: Alemtuzumab for treating relapsing–remitting multiple sclerosis</th>
<th>Section</th>
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<tbody>
<tr>
<td></td>
<td>Key conclusion</td>
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</table>
Alemtuzumab is recommended as an option, within its marketing authorisation, for treating adults with active relapsing–remitting multiple sclerosis.

The Committee considered the manufacturer’s revised base-case results submitted in response to consultation that incorporated all the Committee’s preferred assumptions. The Committee concluded that the most plausible ICER for alemtuzumab compared with glatiramer acetate for people with active relapsing-remitting multiple sclerosis is likely to lie between £13,600 and £24,500 per QALY gained, and therefore alemtuzumab could be considered a cost-effective use of NHS resources for treating adults with active relapsing–remitting multiple sclerosis.

The Committee noted that the most plausible ICER for patients with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment was £8900 per QALY gained for alemtuzumab compared with fingolimod. The Committee noted that for patients with rapidly evolving severe relapsing-remitting multiple sclerosis, alemtuzumab dominated natalizumab (that is, less expensive and more effective).

<table>
<thead>
<tr>
<th>Current practice</th>
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<tr>
<td>Clinical need of patients, including the availability of alternative treatments</td>
<td>The Committee was aware that relapsing–remitting multiple sclerosis is a chronic, disabling, neurological condition that, as it progresses, is life altering and has a large negative impact on quality of life. Currently available first-line treatments for active relapsing–remitting multiple sclerosis need to be injected weekly or several times per week and can be associated with unpleasant side effects. The Committee concluded that any delay in relapse and progression of disability or reduction in the frequency of treatment would have a positive impact on the lives of people with multiple sclerosis and their families. The Committee heard from the clinical specialists that, while therapies should ideally be offered early in disease, offering treatments later in disease is also important because these patients have a higher risk for more severe complications.</td>
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The technology
| Proposed benefits of the technology | The clinical specialists described advantages, including that it is highly effective, does not cause the flu-like symptoms, and does not need to be discontinued by patients planning a pregnancy, although the Committee was aware that effective contraceptive measures should be taken when receiving alemtuzumab and for 4 months following a course of treatment according to the summary of product characteristics. The Committee heard from the clinical specialists and patient expert that alemtuzumab has been a revolutionary treatment for some people, allowing them to live their lives as they had before being diagnosed with multiple sclerosis. | 4.6 |
| How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits? | | |
| What is the position of the treatment in the pathway of care for the condition? | The Committee heard from the clinical specialists that while alemtuzumab's marketing authorisation permits its use as a first-line treatment, it is more likely to be offered to people for whom other disease-modifying treatments have not been effective. One clinical specialist emphasised that alemtuzumab is ‘not for everybody’, and that clinicians would offer alemtuzumab to patients who, among other characteristics, would be likely to comply with the required monitoring. The Committee concluded that alemtuzumab is a valuable treatment option for selected patients with varying types and stages of active relapsing–remitting multiple sclerosis. | 4.4 |
| Adverse reactions | The clinical specialists explained that the main disadvantages of alemtuzumab treatment are the possible serious adverse effects, including idiopathic thrombocytopenic purpura, kidney disease or failure, thyroid disease and death. The Committee concluded that alemtuzumab is associated with significant benefits, but also significant harms, that some people with active relapsing–remitting multiple sclerosis are willing to accept the disadvantages of alemtuzumab treatment, and that adhering to the recommended monitoring schedule is important. | 4.6 |

**Evidence for clinical effectiveness**
<p>| <strong>Availability, nature and quality of evidence</strong> | The Committee considered the clinical effectiveness of alemtuzumab in the relapsing–remitting multiple sclerosis population in the 3 trials comparing it with Rebif. The Committee discussed the manufacturer’s mixed treatment comparison comparing alemtuzumab with other disease-modifying treatments. The Committee was aware that no trials exist that compare alemtuzumab with either natalizumab or fingolimod. | 4.9 |
| <strong>Relevance to general clinical practice in the NHS</strong> | The clinical specialists acknowledged that there was uncertainty regarding the effectiveness of alemtuzumab in the long term, and specifically for periods exceeding the duration of the follow-up studies to the clinical trials. The Committee concluded that for some people alemtuzumab might not provide long-term enduring effect and other treatments might be required. | 4.13 |
| <strong>Uncertainties generated by the evidence</strong> | The Committee concluded that it is more appropriate for the mixed treatment comparison to include all available evidence, and that adjusting for baseline relapse rates accounts for any differences between trials. The Committee noted that in CAMMS223 and CARE-MS II, the investigators used the per-protocol set to conduct the statistical analyses whereas in CARE-MS I the full dataset was analysed, which included some patients who did not meet the specified inclusion criteria or who had not received treatment as specified in the clinical trial protocol. The Committee concluded that it is more appropriate to include the per-protocol analyses set for all 3 trials, adjusted for baseline EDSS states only. The Committee commented that alemtuzumab's clinical effectiveness in the subgroups was not robust. It was aware that no trials exist that directly compare alemtuzumab with either natalizumab or fingolimod. The Committee understood that the mixed treatment comparisons required a number of links to compare alemtuzumab with either natalizumab or fingolimod, and that different trials defined the subgroups differently. | 4.11 4.12 4.14 |</p>
<table>
<thead>
<tr>
<th>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</th>
<th>Acknowledging the uncertainty, the Committee was persuaded that alemtuzumab was at least as effective as fingolimod and natalizumab for people with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment and rapidly evolving severe relapsing-remitting multiple sclerosis respectively.</th>
<th>4.14</th>
</tr>
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<tbody>
<tr>
<td>Estimate of the size of the clinical effectiveness including strength of supporting evidence</td>
<td>The Committee concluded that alemtuzumab is a clinically effective treatment in reducing relapse rates and has a beneficial impact on sustained accumulation of disability at 6 months compared with Rebif in people with active relapsing–remitting multiple sclerosis.</td>
<td>4.9</td>
</tr>
</tbody>
</table>

**Evidence for cost effectiveness**

<p>| Availability and nature of evidence | The Committee considered the manufacturer's revised base-case results submitted in response to consultation. It was aware the manufacturer had incorporated all the Committee's preferred assumptions. | 4.22 |
| Uncertainties around and plausibility of assumptions and inputs in the economic model | The Committee heard that the alemtuzumab trial data and other evidence suggested that people's EDSS states could improve and concluded that it is appropriate for the economic modelling to allow patients to move to lower as well as to higher EDSS states. The Committee considered that the trials provided the most appropriate source of quality of life data because the trial population best reflects the population that would receive the treatment in clinical practice. A number of deaths were observed in the trials and this needed to be reflected in the economic modelling. The clinical specialists also commented that the long-term benefit of alemtuzumab is unknown given the absence of long-term data, but that it would be reasonable to assume that alemtuzumab's treatment effect might start to decrease between 3 and 5 years after treatment. In the trials a further cycle of alemtuzumab was offered to patients if a relapse that lasted for at least 24 hours occurred after the second annual course of infusions, and the clinical specialists commented that further treatments were considered likely in clinical practice. The Committee concluded that it is appropriate to incorporate the time-dependent rate of re-treatment in the model. The Committee concluded that it was more appropriate to remove the mid-cycle correction for the cost of alemtuzumab treatment, increase the number of monitoring and neurology visits to reflect any additional monitoring needed, only include health states costs that are likely to meet the NICE reference case and to include the costs associated with managing adverse effects in the economic modelling. The Committee agreed that it was more appropriate for the manufacturer to use trial data to determine the initial EDSS distribution because this was representative of the patient population likely to be treated with alemtuzumab in the UK. The Committee was also aware that the manufacturer of alemtuzumab has collected data in patients randomised to placebo and concluded that this dataset would more accurately reflect the natural history of disease in people who would be treated with alemtuzumab in the UK. |
| 4.15 | 4.16 | 4.17 | 4.18 | 4.19 |</p>
<table>
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<tr>
<th>Question</th>
<th>Answer</th>
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<tr>
<td>Incorporation of health-related quality-of-life benefits and utility values</td>
<td>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered? The manufacturer pooled EQ-5D-5L utility scores by EDSS state from CARE-MS I and CARE-MS II. The Committee noted that alemtuzumab did provide a step change in the treatment of active relapsing–remitting multiple sclerosis. However, these benefits would already be captured through increased efficacy gains, both in survival gains and in quality of life gains.</td>
</tr>
<tr>
<td>Are there specific groups of people for whom the technology is particularly cost effective?</td>
<td>n/a</td>
</tr>
<tr>
<td>What are the key drivers of cost effectiveness?</td>
<td>The manufacturer's original assumption that the treatment effect from alemtuzumab would persist for many years after the last treatment. The Committee was satisfied that the manufacturer's revised economic analyses adequately explored the sensitivity of the ICER to several scenarios assuming that the effectiveness of alemtuzumab and its comparators waned over time.</td>
</tr>
</tbody>
</table>
Most likely cost-effectiveness estimate (given as an ICER) | The Committee concluded that the most plausible ICER for alemtuzumab compared with glatiramer acetate for people with active relapsing-remitting multiple sclerosis is likely to lie between £13,600 and £24,500 per QALY gained.

The Committee noted that the most plausible ICER for patients with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment was £8900 per QALY gained for alemtuzumab compared with fingolimod. The Committee noted that for patients with rapidly evolving severe relapsing-remitting multiple sclerosis, alemtuzumab dominated natalizumab (that is, less expensive and more effective).

<table>
<thead>
<tr>
<th>Additional factors taken into account</th>
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<tbody>
<tr>
<td>Patient access schemes (PPRS)</td>
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<tr>
<td>End-of-life considerations</td>
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<tr>
<td>Equalities considerations and social value judgements</td>
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</tbody>
</table>
5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has active relapsing–remitting multiple sclerosis and the doctor responsible for their care thinks that alemtuzumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5.3 NICE has developed a costing template and report to estimate the national and local savings and costs associated with implementation.
6  Review of guidance

6.1  The guidance on this technology will be considered for review when the update of NICE technology appraisal guidance 32, NICE technology appraisal guidance 127, and NICE technology appraisal guidance 254 have been published. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
May 2014
7 Appraisal Committee members, guideline representatives and NICE project team

7.1 Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Amanda Adler (Chair)
Consultant Physician, Addenbrooke’s Hospital

Professor Ken Stein (Vice Chair)
Professor of Public Health, University of Exeter Medical School

Professor Keith Abrams
Professor of Medical Statistics, University of Leicester

Dr Ray Armstrong
Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson
Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Professor John Cairns
Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine
Matthew Campbell-Hill
Lay member

Mark Chapman
Health Economics and Market Access Manager, Medtronic UK

Professor Imran Chaudhry
Lead Consultant Psychiatrist and Deputy Associate Medical Director, Lancashire Care NHS Foundation Trust

Dr Lisa Cooper
Echocardiographer, Stockport NHS Foundation Trust

Professor Peter Crome
Consultant Geriatrician and Professor of Geriatric Medicine, Keele University

John Dervan
Lay Member

Dr Maria Dyban
General Practitioner

Robert Hinchliffe
HEFCE Clinical Senior Lecturer in Vascular Surgery and Honorary Consultant Vascular Surgeon, St George's Vascular Institute

Professor Daniel Hochhauser
Consultant in Medical Oncology, UCL Cancer Institute

Dr Neil Iosson
General Practitioner

Anne Joshua
Associate Director of Pharmacy, NHS Direct

Terence Lewis
Lay Member
Dr Miriam McCarthy
Consultant, Public Health, Public Health Agency

Professor Ruairidh Milne
Director of Strategy and Development and Director for Public Health Research at the National Institute for Health Research (NIHR) Evaluation, Trials and Studies Coordinating Centre at the University of Southampton

Dr Elizabeth Murray
Reader in Primary Care, University College London

Dr Peter Norrie
Principal Lecturer in Nursing, DeMontfort University

Christopher O'Regan
Head of Health Technology Assessment & Outcomes Research, Merck Sharp & Dohme

Professor Stephen Palmer
Professor of Health Economics, Centre for Health Economics, University of York

Dr Sanjeev Patel
Consultant Physician & Senior Lecturer in Rheumatology, St Helier University Hospital

Dr John Pounsford
Consultant Physician, Frenchay Hospital, Bristol

Dr Danielle Preedy
Lay Member

Dr Ann Richardson
Lay Member

Dr John Rodriguez
Assistant Director of Public Health, NHS Eastern and Coastal Kent

Cliff Snelling
Lay Member
7.2 **NICE project team**

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Richard Diaz, Martyn Burke**  
Technical Leads

**Joanne Holden, Sally Doss**  
Technical Advisers

**Jeremy Powell**  
Project Manager
8 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Southampton Health Technology Assessment Centre:

- Cooper K, Bryant J Harris P et al., Alemtuzumab for the treatment of relapsing–remitting multiple sclerosis, September 2013

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Manufacturer/sponsor:

- Genzyme

II. Professional/specialist and patient/carer groups:

- Association of British Neurologists
- Multiple Sclerosis Society
- Multiple Sclerosis Trust
- Primary Care Neurology Society
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- United Kingdom Clinical Pharmacy Association
- United Kingdom Multiple Sclerosis Specialist Nurse Association

III. Other consultees:

- Department of Health
• NHS England
• Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

• Biogen
• Commissioning Support Appraisals Service
• Department of Health, Social Services and Public Safety for Northern Ireland
• Healthcare Improvement Scotland
• Merck Serono
• Novartis
• Teva

C. The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on alemtuzumab by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

• Dr Alisdair Coles, University Lecturer and Honorary Consultant Neurologist, University of Cambridge, nominated by Genzyme – clinical specialist
• Sam Colhoun, Clinical Nurse Specialist in Multiple Sclerosis, UK MS Specialist Nurse Association, nominated by the UK MS Specialist Nurse Association (UKMSSNA) – clinical specialist
• Dr Richard Nicholas, Consultant Neurologist and Honorary Senior Lecturer, Imperial Healthcare NHS Trust, nominated by the Multiple Sclerosis Trust – clinical specialist
• Helen Burchmore, nominated by the Multiple Sclerosis Society – patient expert
• Nick Rijke, Director of Policy and Research, the MS Society, nominated by the Multiple Sclerosis Society – patient expert

D. Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.
• Genzyme
About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS.

This guidance was developed using the NICE single technology appraisal process.

It has been incorporated into the NICE pathway on neurological conditions in the multiple sclerosis path along with other related guidance and products.

We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

NICE produces guidance, standards and information on commissioning and providing high-quality healthcare, social care, and public health services. We have agreements to provide certain NICE services to Wales, Scotland and Northern Ireland. Decisions on how NICE guidance and other products apply in those countries are made by ministers in the Welsh government, Scottish government, and Northern Ireland Executive. NICE guidance or other products may include references to organisations or people responsible for commissioning or providing care that may be relevant only to England.

Your responsibility
This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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