NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Alemtuzumab for treating relapsing–remitting multiple sclerosis

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Genzyme	**A1. Relevant evidence has not been considered in describing the expected use of alemtuzumab 12mg (in Section 4.4. of the ACD).** The description of the use of alemtuzumab does not capture that neurology clinical experts expect that alemtuzumab will be used primarily in place of natalizumab and fingolimod for patients with both RES RRMS and HAD despite interferon use. This was indicated in our submission to NICE in the following statements on positioning in STA submission: • PAGE 18 / 52 / 224: "Initially, it is anticipated that alemtuzumab will be used primarily in patients showing a high degree of disease activity (eg. presenting with two or more relapses in the prior year or with one relapse in the prior year despite treatment with interferons or glatiramer acetate) and primarily in place of natalizumab or fingolimod. It should be recognised that the definition of "highly active" for use of alemtuzumab would not need to be as restrictive as that contained within the licences of fingolimod and natalizumab and would be aligned to the more inclusive definition used amongst clinicians in England and Wales treating MS)." • PAGE 239: 73% of those who will receive alemtuzumab 12mg will be patients with RES RRMS or HA disease despite treatment with a beta interferon.	Comments noted.The Committee 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. The Committee concluded that alemtuzumab is a valuable treatment option for selected patients with varying types and stages of active relapsing–remitting multiple sclerosis (see section 4.4 of the FAD).
Genzyme	A3. Relevant evidence has not been considered in the Committee's decision whether alemtuzumab is clinically effective in patients with RES RRMS Two sets of evidence are provided to support the efficacy of alemtuzumab in the RES RRMS subgroups (not reproduced here: *for the full manufacturer's response to the ACD, please refer to the Evaluation report)*	Comment noted. The Committee considered the results of the mixed treatment comparison and the direct evidence for alemtuzumab compared with natalizumab. Acknowledging the uncertainty, the Committee was persuaded that alemtuzumab was at least as effective as natalizumab for people with rapidly evolving severe relapsing–remitting multiple sclerosis (see section 4.14 of the FAD).
Genzyme	A.4 Relevant evidence has not been considered relating to the request to use the TEMSO TOWER placebo arm to derive natural history disease progression	Comment noted. The Committee was aware that the manufacturer of alemtuzumab also

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	transition probabilities for the model in the additional analyses request on page 4 of the ACD	manufactures teriflunomide and has collected data in the TOWER and TEMSO trials, both of which includes groups of patients randomised to placebo. The Committee concluded that it is more 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 disease (see section 4.20 of the FAD).
Genzyme	A.5. Relevant evidence has not been considered to support the inclusion of direct non-health care costs sourced from Tyas et al 2007 within the cost effectiveness analysis which are excluded by using Biogen et al 2007 as requested in the additional information requested in the ACD on page 4 (although the wording "higher health state costs" is used on page 4 this should read "lower health state costs" as confirmed in a telephone call between Genzyme and NICE on 3rd December 2013).	Comment noted. . 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 (see section 4.19 of the FAD).
Genzyme	A.6. Genzyme do not believe that all evidence has been considered in requesting as part of the ACD additional analyses which applies a waning of efficacy solely to alemtuzumab at 3 years and 5 years and not to the comparators as is implied by the wording used in the additional analysis request (on page 4 of the ACD in which "a reduction in efficacy for alemtuzumab starting at 3 or 5 years" is requested without mention of applying waning to the comparators).	Comment noted. The Committee concluded that because of the uncertainty about the long-term treatment effect, it is appropriate to incorporate into the model a 3- and 5-year waning effect for alemtuzumab, and 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

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		time (see section 4.17 of the FAD).
Genzyme	B.1. Genzyme do not believe that the summary of clinical effectiveness which states that alemtuzumab 12mg does not have persuasive evidence that it is clinically effective in HA RRMS despite interferon use patients is a reasonable interpretation of the evidence (Section 4.9. of the ACD).	Comment noted. Acknowledging the uncertainty in the evidence, 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 (see section 4.14 of the FAD)
Genzyme	B.2. Genzyme do not believe that the summary of clinical effectiveness which states that alemtuzumab does not have persuasive evidence that it is clinically effective in RES RRMS patients is a reasonable interpretation of the evidence (as outlined in Section 4.9. of the ACD).	Comment noted. Acknowledging the uncertainty, the Committee was persuaded that the mixed treatment comparison demonstrated that alemtuzumab was at least as effective as natalizumab for people with rapidly evolving severe relapsing–remitting multiple sclerosis (see section 4.14 of FAD).
Association of British Neurologists	The ABN has been asked for its views on the provisional consultation position NICE has indicated concerning alemtuzumab. The ABN unequivocally opposes the provisional position statement indicating that NICE is minded not to approve alemtuzumab for NHS prescription. The vast majority of the concerns raised and detailed information and clarification required by NICE concerning alemtuzumab centre on aspects of modelling: this appears to be directed principally towards the parent company, and we do not believe this to be within our remit. One point of exception would be to draw attention to the peer-reviewed published evidence that alemtuzumab can reduce disability in MS, a positive change that we believe was not accommodated within the models used.	Comments noted. The Committee considered the new evidence submitted by the manufacturer in response to the ACD. The Committee concluded that alemtuzumab could be considered a cost-effective use of NHS resources for treating adults with active relapsing–remitting multiple sclerosis (see section 4.21 of the FAD).
	Additionally, however, the ABN would want to remind NICE that the efficacy data supporting alemtuzumab indicate that it is one of the most potent agents currently available to treat relapsing remitting multiple sclerosis – and we believe the vast majority of MS experts around the world would share this view. It also appears to be the only licensed agent capable of inducing long term remission in MS, i.e. 5 years and possibly longer. We should emphasise that it has been approved and licensed in the EU, and is available and being used extensively outside the UK. To put UK patients in a position of not having access to such an important and effective agent so widely available elsewhere in the EU would be extraordinary; it would have no	Comment noted. 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 Committee concluded that alemtuzumab could be considered a cost-effective use of NHS resources for people with highly active

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	support from the ABN. Finally we would wish NICE in particular to reconsider their extraordinary currently-declared position which appears to accept in principle the evidence for using alemtuzumab in active relapsing-remitting multiple sclerosis, while doubting the case for its use in highly active disease. This may make sense for health economists, but for clinicians this lacks authenticity: recommending a potent drug with significant side effects for patients with modestly active disease but not those whose future is most threatened by their disease would not be a sustainable position; and attempting to synthesise guidelines which recommended a drug for active disease but explicitly exclude those with 'too active' MS would be a challenge as difficult as it was untenable.	relapsing-remitting multiple sclerosis despite beta interferon treatment and people with rapidly evolving severe relapsing-remitting multiple sclerosis (see section 4.22 of the FAD).
MS Society	The MS Society welcomes the opportunity to respond to the ACD for alemtuzumab in treating relapsing remitting multiple sclerosis. We include the views of people with MS as well as those of a number of expert medical advisors specialising in MS. We are very disappointed that the Committee's draft recommendation reports that there is insufficient evidence to support alemtuzumab as a cost effective medicine to be made available in the NHS. We urge NICE to reconsider its decision on alemtuzumab for the treatment of relapsing remitting multiple sclerosis for the following reasons: 1. Potential to significantly enhance quality of life 2. Clinical effectiveness in reducing relapse rates and a beneficial impact on sustained accumulation of disability at 6 months compared with subcutaneous interferon beta-1a 3. Innovative benefits of alemtuzumab 4. Wider benefits of alemtuzumab including enabling a person to live with less requirement for care and support and the potential to remain in work 5. Evidence of cost effectiveness Further details on our reasons are provided here and we also refer NICE to our previous submission on the single technology appraisal of alemtuzumab. **1. Evidence from people with MS** The Committee highlighted that alemtuzumab offers a step change for treating people with relapsing remitting multiple sclerosis, with evidence from clinical specialists stating that it has been a revolutionary treatment for some people, allowing them to live their lives as they had before they were diagnosed with MS (4.14). The MS Society strongly agrees with this opinion. For this reason we ask the	Comments noted. The decision at the first meeting was a 'minded no' that required the manufacturer to present some further economic analysis. The Committee concluded in the FAD that alemtuzumab should be recommended as an option, within its marketing authorisation, for treating adults with active relapsing–remitting multiple sclerosis (see section 1 of the FAD). Comment noted. The Committee concluded that alemtuzumab did provide a step change in the treatment of relapsing–remitting multiple sclerosis (see section 4.24 of the FAD).

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	appraisal committee to take into full consideration and appropriately weight the views and experiences of people with MS. People with MS fear the residual disability a relapse may cause, which can vary from mild to severe, and which is unpredictable in nature. In our survey of more than 1000 people with relapsing remitting MS, 78 per cent said that they always or often worry about how their relapse impacts on those around them; 95 per cent were unable to maintain activities during a relapse and 90 per cent considered that relapses result in a lack of independence. The patient expert giving oral evidence to the Committee stressed that once on alemtuzumab she had not experienced any relapses, with her health being better now than at the time of diagnosis with MS and the considerable impact on her family lessened (4.3). As the Committee states, while alemtuzumab is associated with some risk of serious adverse effects some people with MS are willing to accept this risk because of the treatment's significant benefits (4.7). In light of the Committees' recognition of these benefits, NICE must give due weight to the physical and emotional impact of relapses and not underestimate the potential for this treatment to significantly enhance quality of life.	Comment noted. The Committee concluded that alemtuzumab is associated with significant benefits, but also significant harms, that some people with relapsing–remitting multiple sclerosis are willing to accept the disadvantages of alemtuzumab treatment, and that adhering to the recommended monitoring schedule is important (see section 4.6 of the FAD).
	2. The proven efficacy of alemtuzumab The MS Society agrees with the conclusion of the Committee that 'alemtuzumab was a clinically effective treatment in reducing relapse rates and had a beneficial impact on sustained accumulation of disability at 6 months compared with subcutaneous interferon beta-1a in people with relapsing remitting MS' (4.8). Phase III trials showed alemtuzumab to have a greater clinical effect on reducing relapse rates than any of the current first-line therapies. The MS Society agrees with the clinical specialists that alemtuzumab should be used as a first line option instead of other disease modifying therapies, as well as where other treatments have not been effective and preferably earlier rather than later (4.3). The clinicians pointed out that this would include those who had been on natalizumab and for whom no other treatments are currently recommended. Given this advice and the proven efficacy of alemtuzumab the MS Society sincerely hopes that the Committee will change its current view not to recommend alemtuzumab for rapidly evolving severe and highly active relapsing remitting MS. There is a clear professional consensus that treating people with MS early with the most effective treatment is essential to preserve people's quality of life and as stated in the ACD, 'any delay in relapse and progression of disability … would have a	Comment noted. The Committee heard during the meeting that while alemtuzumab's licence permits its use as a first-line treatment, it is more likely that it would be offered to people for whom other disease-modifying treatments have not been effective. The Committee concluded that alemtuzumab is a valuable treatment option for selected patients with varying types and stages of active relapsing–remitting multiple sclerosis (see section 4.4 of the FAD).

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	positive impact on the lives of people with MS' (4.2). Removing the option of any one effective treatment would be to reduce the possibility that people find a treatment that works for them (in efficacy and tolerance levels) and condemn some people unnecessarily to a life governed by debilitating relapses and the accumulation of disability as well as an increased reliance on health and social care services. **3. The value of innovation** As the Committee is aware, current first line treatments for relapsing remitting MS are administered by injections weekly or several times a week or monthly infusions, while alemtuzumab is an annual intravenous infusion taking 5 consecutive days in the first year and 3 consecutive days 12 months later (some people requiring further infusions in later years). The Committee concluded that a reduction in the frequency of treatment would have a positive impact on the lives of people with MS and their families (4.2) and that alemtuzumab provides a step change in the treatment of relapsing remitting MS (4.14), views with which the MS Society would wholly agree. In addition, alemtuzumab has been shown to reduce the risk of sustained accumulation of disability and also provides the first MS treatment option that does not have to be discontinued for a person to have children (4.7). As the Kennedy report recommended, innovation should be considered and appropriately weighted as part of the decision making process. Alemtuzumab meets many of the health-related benefits criteria listed by Kennedy including: • the ability to offer a different mode of administering a drug – in this case, an annual infusion rather than an injection or monthly infusion for first-line treatment; • improvement in quality of life including enjoyment of greater dignity and independence – this treatment will give people with MS and their carers greater freedom; • the ability to minimise the social visibility of disease or care – an annual infusion is less disruptive than injections required daily or several times a week, or a monthly infusion. It is not clear from the ACD to what extent the above factors have formally been taken into account by the committee, or how each may have been weighted in the decision making process. In our survey, the responses indicated a preference for a therapy that would easily fit in a person's everyday life and normal activities, without debilitating side effects, enabling them to stay in paid employment and to be able to care for their family	Comments noted. The Committee discussed whether alemtuzumab can be considered an innovative treatment and concluded that alemtuzumab did provide a step change in the treatment of 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, in the quality-adjusted life year (QALY) gain. The Committee therefore concluded that no additional QALY gains should be attributed to alemtuzumab to account for these benefits (see section 4.24 of the FAD).

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	rather than being cared for. The Committee heard from the patient expert who gave evidence that alemtuzumab's administration schedule was preferable to weekly or daily self-administered injections with beta interferons, which to her would have been a constant reminder of her MS (4.3). The patient expert also explained that she had been given enough information during the initial stages of treatment to help her understand that monitoring would be essential to prevent adverse events (4.7). **4. Wider benefits of treatment** The ACD concludes that alemtuzumab has the potential to benefit people with relapsing remitting MS and their families (4.3) and that relapsing remitting MS can have a substantial negative impact on quality of life and activities of daily living (4.2). The clinicians told the Committee that the potential benefits of alemtuzumab to quality of life are 'considerable' (4.7). However, there are additional wider benefits of alemtuzumab to which we feel strongly that NICE should give more consideration. As the Kennedy report stated, the wider benefits that should be taken into account include: • ability to join the workforce • staying in work and reducing absenteeism • independence and wellbeing for carers • reduction in social care and welfare costs • increased tax revenue Symptoms of MS, including the emotional and physical impact of MS relapses, have a significant effect on people's ability to care for families and to carry out paid employment. The restriction of this ability during a relapse is of great concern and importance to people with MS. Research has shown that 37 per cent of people in paid employment take more than two weeks off work during a relapse. This evidence is backed up by the Work Foundation Report which found that on average 37 per cent of people with 'mild' MS are working and many more have had to change or quit their jobs due to the fluctuating nature of their MS. It also reported that 44 per cent of people with MS in the UK retire early, in comparison with the 35 per cent European average, and up to 80 per cent of people with MS retire within 15 years of diagnosis, severely shortening the working lives of young adults. Alemtuzumab offers the potential for many people to continue working and to contribute to society. The current first-line options administered by injection can severely restrict people in what they can do, and force affected individuals to reduce their working hours or stop employment altogether.	Comment noted. The Committee concluded that alemtuzumab has the potential to benefit people with active relapsing–remitting multiple sclerosis and their families (see section 4.3 of the FAD).

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	Enabling a person to live more independently, experience fewer relapses and require less care and support would improve their lives as well as their carers'. The Work Foundation report found that 'Professional careers of 57 per cent of relatives are adversely affected by MS of a family member'. The MS Society believes that a wider view must be taken when assessing the cost and benefits of alemtuzumab. **5. Cost-effectiveness** We strongly believe that the evidence supports alemtuzumab as a cost-effective treatment, including the following conclusions from the Evidence Review Group (ERG): • The ERG's own preferred base case approach resulted in alemtuzumab dominating subcutaneous interferon beta-1a (3.28). • All of the ERG's sensitivity analyses showed that alemtuzumab was a cost effective treatment. • The ERG carried out exploratory analyses for the subgroup with highly active relapsing remitting MS despite interferon use, and the subgroup with rapidly evolving severe relapsing remitting MS, and showed that 'alemtuzumab continued to dominate fingolimod and natalizumab' (3.31). Given the potential of alemtuzumab to improve health outcomes without placing a greater burden on the tax payer or the NHS, we believe it would be perverse not to provide this medicine on the NHS.	Comments noted. The Committee considered the EQ-5D-5L data from the alemtuzumab trials which takes into account mobility, self-care, usual activities, pain/discomfort and anxiety or depression (see section 4.16 of the FAD). In addition, the economic model accounted for the disutility of carers (see section 3.14 of the FAD).
	Final comments While the MS Society believes that there is sufficient evidence for the Committee to recommend the use of alemtuzumab, we urge the manufacturer to meet NICE's requests for further clarification and analyses in time for the second Appraisal Committee meeting on 21 January 2014. The available evidence has merited alemtuzumab to be licensed in the EU. The MS Society stresses that it should be made available in line with this licence, without any restrictions for certain populations of people with relapsing remitting MS. If the Committee accepts that alemtuzumab dominates other current options, and given the benefits to patients and the innovative nature of the treatment, this would logically lead the appraisal to reach a positive outcome for people with MS.	Comment noted. The Committee concluded that alemtuzumab could be considered a cost-effective use of NHS resources for treating adults with active relapsing–remitting multiple sclerosis, which includes people with highly active disease despite interferon and rapidly evolving severe disease (see section 4.21 and 4.22 of the FAD).
Multiple Sclerosis Trust	Please find below comments from the MS Trust and UKMSSNA in relation to the Appraisal Consultation Document (ACD) for alemtuzumab, published in December 2013. The ACD states that the Appraisal Committee is minded not to recommend alemtuzumab for the treatment of relapsing-remitting multiple sclerosis (MS).	

Consultee	Comment	Response
	Our submission will address the following areas, as set out in the ACD, namely: a) Has all of the relevant evidence been taken into account? b) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? c) Are the provisional recommendations sound and a suitable basis for guidance to the NHS? d) Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? We do not believe that there are any points relating to item D. All our points relate to the first three items for consideration. The MS Trust and UKMSSNA are extremely disappointed that the Committee is minded not to recommend alemtuzumab for adults with relapsing-remitting multiple sclerosis. Our interpretation of the ACD is that the Committee's concerns centre around two main aspects: • unable to support a recommendation for alemtuzumab in rapidly evolving severe (RES) or highly active despite treatment (HA) subgroups (4.9, 4.22) • unable to determine the cost effectiveness of alemtuzumab compared with other disease-modifying treatments (4.22) Our comments focus on these two major issues. **1. Rapidly evolving severe and highly active despite treatment subgroups** The MS Trust and UKMSSNA is particularly concerned that the Committee is unable to support a recommendation for alemtuzumab in rapidly evolving severe (RES) or highly active despite treatment (HA) sub-groups. With regard to RES and HA, we have commented in previous technology appraisal submissions to NICE that these are artificial sub-groups created to facilitate licensing of natalizumab and fingolimod. In clinical practise, these sub-groups overlap and represent the upper end of a spectrum of disease activity in relapsing-remitting MS, characterised by more frequent and more disabling relapses which may not be controlled by initial treatment with beta interferon drugs or glatiramer acetate. Failure to reduce the number and severity of relapses has a devastating impact both in the short and long term. High disease activity relapsing-remitting MS should be a priority treatment group for disease modifying treatments. These are precisely the patients who have the most to gain from the very effective reduction in relapse rates and stabilisation (and in	Comment noted. The Committee concluded that alemtuzumab could be considered a cost-effective use of NHS resources for treating adults with active relapsing–remitting multiple sclerosis which includes people with highly active disease despite interferon and rapidly evolving severe disease (see section 4.21 and 4.22 of the FAD).

Consultee	Comment	Response
	some cases reversal) of disability seen with alemtuzumab which would offset the greater risk of side effects. This is the group of patients for whom clinicians have been prescribing alemtuzumab off-licence and clinical experience has shown it to be a very effective treatment for these people. Furthermore, the ERG's own exploratory analyses of the cost effectiveness of treating HA and RES sub-groups found that alemtuzumab dominated both fingolimod and natalizumab treatments (3.31). As the treatment paradigm for relapsing remitting MS evolves, there is greater clinical emphasis on induction therapy, dampening down inflammation with a goal of eliminating all evidence of disease activity, both clinical and MRI. Early treatment is therefore key, particularly when there is evidence of aggressive disease. The trade-offs between clinical benefit and burden of potential side-effects and ongoing monitoring may also be more acceptable for patients who have experienced more of the impact of relapses. The Committee heard from specialists about the importance of offering alemtuzumab 'at an earlier rather than a later stage in the disease' (4.4) and also to those 'for whom other disease-modifying treatments have not been effective' (4.4). The exclusion of RES and HA sub-groups from the guidance effectively leaves the very groups who might most benefit from the treatment ineligible. This would not serve the interests of people with relapsing-remitting MS. Given, this, we are surprised that the Committee did not at least request further consideration and analysis of clinical benefit for these sub-groups. No head-to-head trials have compared natalizumab or fingolimod directly with alemtuzumab, but indirect comparison indicates that alemtuzumab has a similar efficacy to these two drugs (3.8). The most substantial use of alemtuzumab off-licence has been in place of natalizumab and fingolimod. **2. Economic model** Our interpretation of the ACD is that the Committee's concerns centre on uncertainty over the manufacturer's economic model and felt it was unable to determine the cost effectiveness of alemtuzumab compared with other disease modifying treatments (4.22). The Committee has presented a series of questions for the manufacturer but has not been clear about the implications of the results of the additional analyses or what further evidence this is expected to provide. We recognise that a key responsibility of the Committee is to establish whether a new treatment represents a cost-effective use of NHS resources. Our own reading of the ACD, both from the summaries of the manufacturer's submission and the ERG comments, would suggest that certain changes made by the ERG to the economic model resulted in alemtuzumab dominating (being less costly and more	Comments noted. The Committee concluded that alemtuzumab was a valuable treatment option for selected patients with varying types and stages of active relapsing-remitting multiple sclerosis (see section 4.4 of the FAD). Comments noted. 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 (see section 4.14 of the FAD). Comment noted. The Committee considered the manufacturer's revised base-case results for the active relapsing–remitting multiple sclerosis population submitted in response to consultation which had incorporated all the Committee's preferred assumptions. The Committee concluded that alemtuzumab could be considered a cost-effective use of NHS resources for treating adults with active relapsing–remitting multiple sclerosis (see section 4.21 of the FAD).

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	effective than interferon beta-1a) with a cost saving of £852 per QALY gained (3.28). Further manipulation of the economic model generated ICERs per QALY gained of £1013 to £8336 (3.29), elsewhere described as mostly below £10,000 (4.22). This falls well within the NICE QALY threshold of £20,000-30,000. However, further manipulating the economic model to create a worst case scenario generated an ICER of £1,200,000 (4.22). In all the NICE technology appraisals for multiple sclerosis disease modifying drugs, the health economics of MS have proved very difficult to model. How do the assumptions behind this worst case scenario reflect a real world situation? Should an extreme outcome of this sort be disregarded or should it disallow evidence which clearly demonstrates value for money to the NHS? The Committee acknowledges that alemtuzumab's administration schedule and reduction in relapse rates represents a "step change in the treatment of relapsing-remitting multiple sclerosis" (4.14). Furthermore, the Committee concluded that "on the basis of improvements in sustained accumulation of disability at 6 months in the trials and in relapse rates, alemtuzumab was a more clinically effective treatment for relapsing-remitting MS than subcutaneous interferon beta-1a" (4.8). The ERG's own analyses in different scenarios found that alemtuzumab dominated or gave ICERs of less than £10,000 compared to interferon beta 1a. On the face of that evidence, that the drug is clinically effective and cost-effective, that is has a positive effect on health outcomes and delivers value for the health service, it seems perverse that NICE would not recommend the drug for use in the NHS. 3. People with relapsing-remitting multiple sclerosis currently have very limited treatment options. The committee heard from both clinical and patient experts about the importance of access to a range of medicines, particularly for those who are unable to tolerate current treatments which are associated with significant side effects as well as injection site reactions. Despite the overall efficacy of current treatments for preventing MS relapses, any one of them can simply fail to work in a particular patient, or cause debilitating side effects. Clinicians lack tools to predict who would respond well to a specific therapy. Four of the five current first line treatments (Avonex, Betaferon, Extavia and Rebif) have the same mechanism of action. If a patient fails to respond to one of these drugs or develops side effects, glatiramer acetate is the only alternative treatment with a different mechanism of action. All of the current first line treatments are self-injected. Through supporting people who are taking the current first line treatments, the MS Trust is aware that the requirement for long-term injections places a burden on them and in some cases	Comment noted. The Committee 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 Committee 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 people with rapidly evolving severe relapsing-remitting multiple sclerosis (see section 4.22 of the FAD).

Consultee	Comment	Response
	leads to a decision not to start treatment, delays initiating treatment or results in reduced adherence. Self-injecting is painful, results in anxiety and stress; can lead to skin reactions and complications at injection sites; may be difficult for people whose manual dexterity is limited, requiring help from carers and families; and imposes restrictions on a number of aspects of general living. Alemtuzumab has a unique administration schedule, it acts in a different way to the current disease modifying drug therapies, and has a different profile of side effects. It will significantly enhance the range of treatments available to people with relapsing-remitting MS, providing a genuine alternative to the current therapies. **Conclusion** As stated in the ACD, clinical specialists considered that in clinical practice, alemtuzumab would be used instead of other disease modifying treatments and preferably at an earlier rather than a later stage in the disease (4.4). Alemtuzumab would also be offered to people for whom other disease modifying treatments have not been effective and for whom there are no other treatment options currently recommended. Alemtuzumab has efficacy greater than current first line treatments (beta interferon drugs, glatiramer acetate and teriflunomide), and approximately equivalent, or greater, efficacy than fingolimod and natalizumab. The Committee heard from clinical experts (4.4) that alemtuzumab is "not for everyone" and acknowledges that some people are willing to accept the risks of alemtuzumab treatment and adhere to the monitoring schedule (4.7). The committee concluded that alemtuzumab would be a valuable treatment option for selected patients. Research evidence demonstrates the importance of active, early treatment of relapsing-remitting MS to prevent axonal damage and avoid irreversible disability. The European Commission has licensed alemtuzumab for active relapsing-remitting MS, defined by clinical or MRI features. The difficulty in calculating cost effectiveness of MS drugs is well recognised, particularly as the trial data does not address the long term benefits of treatment. The MS Trust encourages the Committee to recognise that alemtuzumab would be an important addition to the small range of available disease modifying therapies for MS. As with other disease modifying therapies, alemtuzumab should be prescribed by neurologists, with commencement of therapy and ongoing monitoring provided by specialist MS nurses.	

The Department of Health and Royal College of Pathologists had no comments on the appraisal consultation document for alemtuzumab.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Patient expert nominated by Shift MS	My name is [redacted] and I am aged 31. I was diagnosed with relapsing remitting multiple sclerosis (MS) in 2004. I started on interferon beta-1a (Rebif) in 2005, however, due to the frequency and severity of my relapses, it was agreed that highly-effective treatment would be the most appropriate way of managing my condition. In 2006, I had a course of mitoxantrone in combination with glatiramer acetate (Copaxone). The effects of mitoxantrone began to wear off and I had several aggressive relapses. In 2011 I began on natalizumab (Tysabri). In October 2013 I discovered that I had converted to being JC virus positive and was strongly advised to stop taking natalizumab, as my previous immunosuppressant use and the 24+ monthly natalizumab infusions meant I was now in the high risk category for contracting the rare and sometimes fatal viral brain disease, progressive multifocal leucoencephalopathy (PML). I have spoken with my neurologist in Leeds, along with leading MS specialist neurologists in London and Cambridge who have all advised that, to keep my MS in remission, alemtuzumab is the only comparable alternative to natalizumab. I am writing to strongly urge NICE to make alemtuzumab available to patients with active relapsing remitting MS in the UK, including patients in similar exceptional circumstances who due to being in the high risk category have been forced to stop taking natalizumab. I am currently leading a normal life, working full time and am desperate for this to continue. I am terrified about what could happen, and the societal burden I may become, if I was left with no option but to take a treatment with lower efficacy.	Comments noted. The Committee concluded that alemtuzumab could be considered a cost-effective use of NHS resources for treating adults with active relapsing–remitting multiple sclerosis and for adults with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment and adults with rapidly evolving severe relapsing-remitting multiple sclerosis (see section 4.21 and 4.22 of the FAD).
Clinical expert nominated by Genzyme	Thank you for asking me to comment on the appraisal consultation document for the Single Technology Appraisal of Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis. In answer to the specific questions asked, all of the relevant evidence has <u>not</u> been taken into account; the summaries of clinical effectiveness are <u>not</u> reasonable interpretations of the evidence; and the provisional recommendations are <u>not</u> a sound and a suitable basis for guidance to the NHS. I agree that the further analyses requested by NICE of the manufacturer in	Comment noted.

Nominating organisation	Comment	Response
	1.2 of the ACD are reasonable and helpful. My concern is with the committee's assessment of the clinical effectiveness of alemtuzumab. I agree with its conclusion, in 4.8, that alemtuzumab is a more effective treatment for relapsing–remitting multiple sclerosis than subcutaneous interferon beta-1a and that it represents a "step change in the treatment of relapsing–remitting multiple sclerosis" (4.14). However, the decision (4.9) that alemtuzumab should not be recommended for rapidly evolving severe multiple sclerosis and highly active relapsing–remitting multiple sclerosis despite interferon is not logical, fails to consider the totality of the evidence and contradicts the licence granted by the European Medicines Agency, and contemporary concepts on the treatment of multiple sclerosis which has established that initial severity of disease predicts disability and requires early intervention with the most effective therapies. The committee bases its view of alemtuzumab's efficacy in these two disease subgroups entirely on the mixed treatment comparisons reported in 3.8 which showed lower relapse rates on alemtuzumab treatment than either fingolimod or natalizumab, albeit without statistically significant differences. I recommend that the committee also take into consideration these three points: 1. In phase 2 or phase 3 trials, neither fingolimod nor natalizumab have shown superior efficacy to interferon in terms of preventing the accumulation of disability in multiple sclerosis, which is a more important outcome for patients than relapse rate. Yet alemtuzumab has achieved this threshold in one phase 2 and one phase 3 trial, for all included patients and for those fulfilling the definition of rapidly evolving multiple sclerosis (see Table B6.5.6 of the manufacturer's submission). 2. Even if alemtuzumab had only equivalent efficacy to fingolimod or natalizumab in the active multiple sclerosis subgroups, it would be an attractive alternative for several groups of patients, for instance women wishing to become pregnant (not possible whilst under on treatment with fingolimod or natalizumab) or those who fear the risk of progressive multifocal leucoencephalopathy following natalizumab (which may be as high as 1/90 for those with positive	Comment noted. The Committee noted that the CARE MS-II study comparing alemtuzumab with subcutaneous interferon beta-1a showed that alemtuzumab had a greater treatment effect in people with rapidly evolving severe disease than fingolimod had in the FREEDOM study when compared with placebo. Similarly, the Committee noted that the CAMMS223, CARE MS-I and II studies comparing alemtuzumab with subcutaneous interferon beta-1a showed that alemtuzumab had a greater treatment effect in people with highly active disease despite interferon treatment than natalizumab had in the AFFIRM study when compared with placebo. 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 (see section 4.14 of the FAD).

Nominating organisation	Comment	Response
	JC virus serology after two years of natalizumab therapy). 3. As the committee recognises, alemtuzumab is a more efficacious drug than interferon with a potentially serious safety profile which needs careful management. It is therefore illogical, and defies the available evidence from clinical trials, to endorse its use as first-line therapy but not to more aggressive forms of multiple sclerosis that have either failed to be controlled on interferon, or for whom interferon is considered futile. Please note that conservative decision-makers, such as Health Canada and a few individuals within the Committee for Medicinal Products for Human Use of the European Medicines Agency (as noted in 4.13), have taken the opposite view, proposing that alemtuzumab should be reserved for those with continued disease activity on interferon and other multiple sclerosis therapies. Indeed, I imagine that most neurologists in the UK would –if permitted- first use alemtuzumab in this situation in place of natalizumab or fingolimod; Genzyme estimate >70% alemtuzumab will initially be used for rapidly evolving severe multiple sclerosis and highly active relapsing–remitting multiple sclerosis. However, over time, as physicians become comfortable with handling the drug and monitoring programme, I anticipate that – if permitted – increasing proportions of treatment-naïve patients will receive the drug.	Comment noted. The Committee concluded that alemtuzumab is associated with significant benefits, but also significant harms, that some people with relapsing–remitting multiple sclerosis are willing to accept the disadvantages of alemtuzumab treatment, and that adhering to the recommended monitoring schedule is important (see section 4.6 of the FAD).
Patient expert nominated by MS Society	Thank you for sending me the consultation documents for the appraisal of Alemtuzumab for relapsing-remitting multiple sclerosis. I'm afraid that despite the best efforts of both [redacted] I was unable to open the Evaluation report and so my comments are limited to the ACD itself – I hope that is alright. I have also spoken to the team at the MS Society who were kind enough to put me forward as their patient expert for this consultation, and find myself in full and enthusiastic agreement with their statement. Obviously their response is an extremely well-considered and professional response; I hope that this email is sufficient as the response of a patient to the Committee's decision.	Comments noted. The Committee concluded that alemtuzumab could be considered a cost-effective use of NHS resources for treating adults with active relapsing–remitting multiple sclerosis and for adults with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment and adults with rapidly evolving severe relapsing-remitting multiple sclerosis (see section 4.21 and 4.22 of the FAD).

Nominating organisation	Comment	Response
	I am hugely disappointed to hear of the initial decision of the Committee following a long meeting discussing the benefits of alemtuzumab to patients with RRMS. From a personal perspective as a person with relapsing-remitting multiple sclerosis who has received treatment with alemtuzumab I can attest to the huge benefit of treatment for my condition, allowing me to be in better health (physical and mental) six years following my last regime than I was at diagnosis or for the eighteen months following. At diagnosis my MS was both rapidly evolving with fresh symptoms occurring frequently, and highly active – and the difference treatment made has been huge. Alemtuzumab really does have significant positive effects on the disease, and they last for a significant length of time. I believe that the Committee has been slightly mistaken in some of its conclusions. I fully understand the necessity of placing the majority of the focus for decision-making on the cost-effectiveness of a new treatment in order to make recommendations to the NHS – as a 'free at the point of delivery' service, the NHS must absolutely ensure that any drug it is allowed to use provides maximum patient benefit for as long as possible, with as few side-effects or harms as possible and for as low a cost as can be arranged – but I believe that in their initial decision the Committee have placed themselves in the difficult position of having to explain to the MS community (not only here but worldwide, in light of similar decisions being made globally) why the ability of a MS patient to choose a treatment has been curtailed. The newly revised NHS Charter outlines the rights of patients to be given choice in their treatments, and by not recommending alemtuzumab this choice is then limited to the currently existing drugs, many of which do not provide the long-term benefits or convenient treatment schedule of alemtuzumab. As people also tend to be diagnosed with active disease, then allowing the use of alemtuzumab as a first-line treatment would be the best possible outcome – treating the condition early in its progress and limiting the accumulation of disability from early relapses is paramount for continuing a normal life into the future. If alemtuzumab is not licensed for use in the NHS, a situation of potential discrimination is also established. As the drug has been licensed by the European Medicines Agency then it is available for those with private	

Nominating organisation	Comment	Response
	healthcare arrangements, allowing those with the necessary finances to receive the drug while still continuing to exclude others who may need it. I appreciate that 'fairness' is not an economically valid argument, but as those who are diagnosed with MS go on to suffer from other economic penalties such as health-related early retirement, increased levels of unemployment and costs associated with care, improvements to living conditions etc it seems unduly harsh to add 'effective treatment only for those who can pay' to the list. Having actually had treatment – having sat in a hospital bed with a cannula dripping alemtuzumab into a vein, having suffered from sweats, chills, rigours and rashes, and having gradually realised over the course of a few weeks post-treatment how well I felt, I think I can say that the Committee has also overstated the side-effects of treatment. As I explained in my initial patient expert statement, the treatment does indeed have some immediate adverse effects; however these take place in hospital during treatment, and are easily treated at that point. None were bad enough in the first year of treatment to dissuade me from returning for a second year of treatment. The long-term side-effects, such as the development of other autoimmune conditions, can be spotted with the regular blood testing and if the patient is compliant, can be treated as they arise. I realised during the first meeting of the Committee that the list of side effects preyed heavily on people's minds, but there are few MSers I have spoken to who would find anything on that list more problematic than their existing condition. Again, it is about choice – people with MS need to be trusted to understand the cost-benefit ratio as it applies to their own experience of the condition. They know whether the disease or the treatment would be worse for them on an individual level, and must be allowed to make their choice – either way. If the focus, of necessity, has to be on health economic grounds, then perhaps the true cost of the disease across a life-course needs to be explored, including periods of unemployment, social and care costs, other medications such as for depression and anxiety as well as the rippled-out costs and pressures on family and friends. The cost of the drug would be high if it didn't work so well and offer such long-term benefits, but set against the cost of treating relapses and deterioration in a patient, the cost seems reasonable to those of us who live with the condition. As there are so few effective treatments for MS currently available, it is surely necessary to	Comments noted. Please note that the 2008 NICE Guide to the Methods of Technology Appraisal (paragraph 5.2.7) that *"the perspective adopted on costs should be that of the NHS and PSS. Technologies for which a substantial proportion of the costs (or cost savings) are expected to be incurred outside of the NHS and PSS, or which are associated with significant non-resource effects other than health, should be identified during the scoping stage of an appraisal. In these exceptional*

Nominating organisation	Comment	Response
	licence a new one that could benefit so many more patients, especially if given as a first-line treatment to protect against early disability accumulation.	*circumstances, information on costs to other government bodies, when these are not reflected in HRQL measures, may be reported separately from the reference-case analysis.*

Comments received from commentators

Commentator	Comment	Response
Biogen	We have not used the tabulated format as our comments are general and we have not re run the model to produce results based upon these comments. However, we feel that re analysis incorporating the changes suggested by these comments would be desirable. **Alemtuzumab for treating relapsing forms of multiple sclerosis [ID539]: Manufacturers Model** Biogen Idec would like to thank the National Institute for Health and Care Excellence (NICE) for the opportunity to review and comment on the Appraisal Consultation Document (ACD) for alemtuzumab for treating relapsing forms of multiple sclerosis. Our comments are in relation to the robustness of the health economic model for alemtuzumab, whereby we support the case for additional analysis to be conducted in order to reduce the uncertainty around the clinical and cost-effectiveness of alemtuzumab, when compared to other available treatments. **MODEL STRUCTURE** The overall structure appears consistent with previous models used in previous NICE appraisals based on EDSS; however, we note that the structure does not allow for the regression of disability between EDSS states. Excluding regression will result in the patient population progressing more rapidly to higher EDSS states and SPMS than it would be expected under real-world conditions. This has an impact on the reliability of the ICER of alemtuzumab versus other available comparators. **MTC RESULTS** The hazard ratios and relative rates of relapses are difficult to interpret and threaten	Comments noted. Comment noted. The Committee agreed 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 both improve and get worse, which is in line with what is seen in clinical practice for the lower EDSS states (see section 4.15). Comment noted. The Committee acknowledged the

Commentator	Comment	Response
	the face-validity of the model; for example, the hazard ratio for Betaferon is 1.21, with BSC 1.0. Particular attention should be paid to the results showing interferon1-b having worse clinical outcomes than BSC. Further, the MTC treatment effects do not appear to be consistent with the head-to-head studies available, which threatens the predictive validity of the MTC.	limitations of the MTC presented by the manufacturer The Committee agreed that the 'all years' MTC adjusted for baseline relapse rates was appropriate (see section 4.11 of the FAD).
	MONITORING AND ADMINISTRATION ASSUMPTIONS. Assumptions on the use of resources for the monitoring and administration of alemtuzumab appear reasonable. However the monitoring has not allowed any MRI costs for alemtuzumab, which would be expected especially in the first year. It is recommended that MRI be considered for inclusion in the model for alemtuzumab including any associated costs such as a neurology visit.	Comment noted. The manufacturer included the cost of an annual MRI in its additional analyses in response to the appraisal consultation document (see page 16 of Manufacturer's Additional Analysis and section 3.32 of the FAD).
	ADVERSE EVENTS The adverse events rates unduly bias in favour of alemtuzumab. A comprehensive and transparent list of adverse events for alemtuzumab should be provided and included in the MTC analyses by the manufacturer. In particular the adverse event rates for human papillomavirus infection, including cervical dysplasia (2%) and superficial fungal infections (12%) should be considered. The long term effects of alemtuzumab on immune function and the potential for thyroid malignancy is unknown but could potentially incur additional costs and disutility. Long-terms results for a cohort of patients are available but unpublished. These should be incorporated to validate the predictive aspect of the model.	Comments noted. The Committee concluded that it would be more appropriate for the analyses to include the trial data, which provided more realistic values for the disutility of adverse events associated with alemtuzumab. See section 4.16 of the FAD. The Committee concluded that alemtuzumab is associated with significant benefits, but also significant harms, that some people with relapsing–remitting multiple sclerosis are willing to accept the disadvantages of alemtuzumab treatment, and that adhering to the recommended monitoring schedule is important (see section 4.6 of the FAD).
Novartis	Novartis would like to thank the National Institute for Health and Care Excellence (NICE) for the opportunity to respond to the draft appraisal consultation document (ACD) for alemtuzumab. We would also like to commend NICE for their overall rigorous approach to the consideration of the evidence and the request for extensive additional economic analyses in this case, which we feel are wholly justified given the evidence presented for this therapy.	Comments noted.
	We do have several points that we would like to raise with the Committee, however.	Comment noted. Although fingolimod and natalizumab were included in the manufacturer's

Commentator	Comment	Response
	The most important of these relate to the populations that are used in the comparison of alemtuzumab to fingolimod and the additional analysis requested on long-term retreatment rates. Please find our points detailed below: **1. <u>Populations used in the Comparisons to Fingolimod</u>** <u>Inappropriate consideration of fingolimod</u> The manufacturer's submission for alemtuzumab is based around first line treatment of the active RRMS population, defined by this therapy's marketing authorisation. This does not represent the same population for which fingolimod is licensed and recommended by NICE: patients with <u>highly</u> active RRMS despite beta interferon treatment. The manufacturer's economic analysis for alemtuzumab versus fingolimod and natalizumab uses the whole RRMS population and compares the treatments as first line (Section 3.17), which is inappropriate given fingolimod's marketing authorisation and NICE recommendation as described above. Although it is reported that the manufacturer does acknowledge that fingolimod and natalizumab are restricted by their marketing authorisations to the specific high disease activity subgroups, we feel that it is still inappropriate and misleading to report the results of the whole RRMS first line comparison within the ACD and request that this is removed from the report. <u>Validity of the subgroup analysis of alemtuzumab</u> We are pleased to read that the Committee has critically appraised the quality and reliability of the subgroup analysis for alemtuzumab in patients with highly active disease. We would ask that further details of this subgroup analysis, such as the sample sizes, are made available within the ACD so that readers can appraise the reliability themselves and understand how the Committee came to their decision. **2. <u>Long-term Retreatment Inputs</u>** It was acknowledged in the ACD that the manufacturer's inputs for retreatment in the economic model may not reflect the situation in actual clinical practice. We are glad that NICE have requested that the manufacturer investigate this important issue further. The ACD states that "The Committee heard from the clinical specialists that in the trials, the percentage of people who needed a third course [of alemtuzumab] was	incremental analysis, the manufacturer included these for completeness and acknowledged that these drugs have marketing authorisations only for use in highly active disease despite interferon treatment and rapidly evolving severe disease (see section 3.17 of the FAD). Comment noted. The CAMMS03409 extension study which enrolled people with RRMS from the

Commentator	Comment	Response
	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)." We have a few concerns over this statement:	CAMMS223, CARE-MS I and II trials has a median follow-up of 7 years (see section 3.1 of the FAD).
	a) Firstly, we are not aware of trial data for alemtuzumab that extends to 7 years, so would hope that the Committee is planning to look carefully into the source of this data, including the methodology of its collection, the potential biases that may occur, the sample size and the patient characteristics. We feel that it would be appropriate for a brief appraisal of this data source and its limitations to be included in the final report.	Comment noted. 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 (see section 4.18 of the FAD).
	b) Secondly, we are unsure how the Committee is interpreting the need for a "time-dependent rate of re-treatment" in their request for this to be applied in the model. We agree that the rate of re-treatment is likely to be time-dependent: the risk of requiring a retreatment with alemtuzumab is expected to increase over time spent on treatment. This is supported by Alisdair Coles' statement that more patients would experience relapses and hence require re-treatment towards the end of the 7 year period than in years 3 or 4. We hope, therefore, that the Committee has requested an increasing rate of re-treatment over time, rather than a decreasing one. We note that this does not preclude a trend for fewer people needing successive courses, as is also supported by the evidence; it simply means that following each course, there will be a time-dependent increasing rate of re-treatment.	Comments noted. See above.
	c) Thirdly, we would like to clarify our concern over whether the reference to 7 year data prevents re-treatments after 7 years from being included in the model. Whilst we acknowledge that retreatment rates in the long term are uncertain due to the lack of long-term data, some retreatment beyond 7 years would be expected and we feel that this should be investigated in the economic model. In cases of uncertainty, we were under the impression that conservative assumptions should be applied, which in this case would be a high retreatment rate in the long term (ie. beyond 7 years).	

Commentator	Comment	Response
	3. <u>Monitoring</u> We have several points for consideration with regards to monitoring costs and adherence to monitoring: a) We are surprised that the monitoring costs for alemtuzumab used in the model are reported as lower than those for fingolimod and natalizumab for year 1, and lower than all DMTs, including beta-interferon and glatiramer acetate, in years 2+. This does not appear consistent with the extent of discussion on monitoring requirements for alemtuzumab at the NICE Committee meeting where all the clinical experts agreed that monitoring is a considerable issue. For example, the risk of experiencing a serious thyroid adverse event with this therapy was noted as increasing from years 2 – 4, which appears to contradict lower monitoring costs in year 2. The summary of product characteristics for alemtuzumab specifies several laboratory tests that should be performed for patients who have received this treatment. These have been costed by the manufacturer (as outlined in the manufacturer's submission), but given the views of the clinical experts, it seems likely that there are additional monitoring costs that have not been accounted for by the manufacturer. b) We are disappointed that the ERG has presented its monitoring requirements of 4 visits in the **first year** and 2 annually thereafter as "a worst case scenario". Alasdair Coles noted that monitoring would in fact be higher than this (4 visits in the first **2 years**, then 2 visits annually with monitoring reset upon retreatment). If this is the monitoring that is required to offset the risks associated with use of alemtuzumab then this input should represent the base-case of the appraisal and not be presented as the "worst case".	Comment noted. In the manufacturer's original submission, it assumed that there would be 2 neurology visits in the first year and 1 neurology visit in the subsequent years (see table B7.5.4 in the manufacturer's original submission). The Committee concluded that there should be increased monitoring and neurology visits for patients treated with alemtuzumab as well as visits for monitoring after restarting alemtuzumab treatment (see section 3.33 of the FAD). In the manufacturer's additional analyses, the monitoring for alemtuzumab was increased to 4 neurology visits in the first year and 2 neurology visits thereafter and the number of MRIs increased to 1 per year (see manufacturer's additional response Data Request 11). The Committee considered the manufacturer's revised base-case results for the active relapsing–remitting multiple sclerosis population submitted in response to consultation and noted that the manufacturer had incorporated all the Committee's preferred assumptions. The Committee concluded that alemtuzumab could be considered a cost-effective use of NHS resources for treating adults with active relapsing–remitting multiple sclerosis (see section 4.21 of the FAD).
	c) If adherence to monitoring is not maintained, which is highly likely according to both clinical experts and patient experts, then side-effects may well be above those seen in clinical trials and incorporated in the manufacturer's model. A further consideration is that monthly monitoring may well not identify all serious side-effects of the drugs, for example because platelet	Comments noted. The Committee concluded that alemtuzumab is associated with significant benefits, but also significant harms, that some people with relapsing–remitting multiple sclerosis are willing to accept the disadvantages of alemtuzumab

Commentator	Comment	Response
	counts can drop very suddenly in the period between monitoring visits. We are unclear whether the model captures these risks. d) Given the uncertainty over both the long-term safety implications of alemtuzumab and the extent of adherence to monitoring that will occur in clinical practice, we propose that, should a positive recommendation for alemtuzumab ultimately be provided, NICE consider recommending that a dedicated registry is set up to ensure that all safety signals in patients treated with this therapy are captured and analysed (as has been done in previous cases, such as in TA103). This would be the only way for the NHS to be confident that they are adequately monitoring a therapy that could have very serious long term side effects that are currently unknown. Furthermore, given that there is 7 years of clinical experience for alemtuzumab available from UK patients, it would also seem advisable to perform a retrospective review of this data from a pharmacovigilance perspective. The need to understand more fully the safety profile of alemtuzumab has been highlighted in the recent Food and Drug Administration (FDA) assessment report of this intervention in the USA. **4. <u>Additional Points for Consideration</u>** We are pleased to see that the Committee is considering issues regarding renal complications and post-alemtuzumab treatment with bone marrow transplant (BMT). We have provided some additional points for consideration below on each of these topics, which may aid future discussions. We also note below a clarification over definitions of high disease activity subgroups. <u>Renal complications</u> We agree with the Committee that given the clinical experts' concerns over renal complications, these should be included within the economic model. We have noticed, however, that the request for analysis focusses only on including the additional **costs** of renal complications. We hope that the **utility** implications of such serious adverse events are also being considered. <u>Bone Marrow Transplant</u> It was noted that bone marrow transplant (BMT) is the treatment option most likely	treatment, and that adhering to the recommended monitoring schedule is important (see section 4.6 of the FAD). Comments noted. See above. Comment noted. Comments noted.

Commentator	Comment	Response
	to be employed following a lack of success with alemtuzumab. We would like to highlight that this is an expensive treatment option and one associated with considerable morbidity and mortality. We are concerned over the impact of introducing alemtuzumab as a routine treatment, where there is a possibility that the routine following treatment would be such a drastic intervention as BMT. We also hope that the full costs of BMT (approximately £30,000 per procedure in the UK) and disutility will be incorporated into the model. <u>Definitions of high disease activity subgroups</u> It has come to our attention that the ACD does not fully define the high disease activity subpopulations for which fingolimod and natalizumab are indicated and recommended. As not all readers of the ACD will be familiar with the difference between highly active disease despite beta-interferon and rapidly evolving severe RRMS, we would suggest it might be beneficial to clarify the full definitions by providing in the ACD the definitions presented in TA127 and TA254, or by referring to these previous technology appraisals in which the full definitions can be found. **Summary** Novartis are reassured to see that the Committee has critically appraised the evidence for alemtuzumab and requested many important additional economic analyses. To summarise the main points that we would like to raise to the Committee following review of the ACD: • There are cases within the ACD where fingolimod has been considered in a population outside of its marketing authorisation, namely in a first-line population and in the whole RRMS population. • In terms of long-term re-treatment, we hope the Committee will appraise the source of evidence for 7 year exposure as cited by the clinical expert and consider the increased risk of re-treatment over time. We were surprised that for the monitoring costs used by the manufacturer, the cost for alemtuzumab used in the model was reported as lower than that for fingolimod and natalizumab for year 1, and lower than all DMTs, including beta-interferon and glatiramer acetate, in years 2+, which does not seem consistent with the discussions held at the appraisal meeting. Additionally, the ERG has included a lower estimate for neurology visits for alemtuzumab patients in their worst case than	

Commentator	Comment	Response
	is expected in clinical practice as stated by one of the clinical experts.	
Royal College of Nursing	**Introduction** The Royal College of Nursing (RCN) was invited to review the Appraisal Consultation Document (ACD) for **Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis** The document was circulated to nurses who care for people with multiple sclerosis for their views. **Appraisal Consultation Document – RCN Response** The Royal College of Nursing welcomes the opportunity to review this document. The RCN's response to the questions on which comments were requested is set out below: i) **Has the relevant evidence been taken into account?** The summary of the evidence review seems reasonable.	Comment noted.
	ii) **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Cost effectiveness: There seems to be a great disparity between the figures. On the one hand the model suggests that the cost is in the region of £10,000 (low enough for NICE to recommend this treatment as it costs less than the 20 - 30 k threshold), however, later it discusses a cost of over a million pounds. This is a tremendous leap and could lead to some confusion or misinterpretation. We would suggest that clarity is definitely required in this area in order to truly give an unbiased view.	Comment noted. The summary of the cost effectiveness evidence presented by the manufacturer and reviewed by the ERG included a range of ICERs. These ICERs had a wide range, reflecting the uncertainty within the model presented by the manufacturer. In the FAD, the Committee concludes which are the most plausible for each of the populations presented (see sections 4.21 and 4.22 of the FAD).
	iii) **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** We note the recommendation that the committee is not minded to recommend the use of this health technology for the target population, that is, for treating adults with relapsing–remitting multiple sclerosis with active disease defined by clinical or imaging features. We also note that the Committee has recommended that NICE requests further clarification and analyses from the manufacturer on various points, to be made available for the second Appraisal Committee meeting. We	Comment noted.

Commentator	Comment	Response
	welcome this. We note that the manufacturer has marketing authorisation for the technology to be used in highly active disease i.e. in line with Tysabri and Gilenya. We would ask that the committee in considering the further information it is requesting from the manufacturers, also reviews and reconsiders the decision that the drug should not be given in the highly active or rapidly progressing MS. We would ask that any guidance issued is in line with the current clinical pathway.	Comment noted. The Committee concluded that alemtuzumab could be considered a cost-effective use of NHS resources for treating adults with active relapsing–remitting multiple sclerosis and for adults with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment and adults with rapidly evolving severe relapsing-remitting multiple sclerosis (see section 4.21 and 4.22 of the FAD).
	iv) **Are there any aspects of the recommendations that need particular consideration to ensure that NICE avoids unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** We are not aware of any specific issue at this stage. We would ask that any guidance issued should show that an equality impact analysis has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.	Comments noted. Equalities issues are identified and considered by the Committee at every stage of guidance development. The Committee considered whether the monitoring requirements imposed on alemtuzumab by the regulatory authorities raised a potential equality issue for people with active relapsing–remitting multiple sclerosis. The Committee concluded that this was not an equality issue as the monitoring requirements are a safety issue which apply to everyone being treated with alemtuzumab, regardless of disability status (see the Summary of Appraisal Committee's key conclusions in FAD).

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional	3	The evaluation of clinical effectiveness focuses mainly on the EDSS score which does not capture other symptoms such as fatigue, bladder symptoms, cognitive impairment and depression. We agree with the criticism of the ERG that trial data before 2000 was excluded in the base-case analysis. We are also in agreement with the concern regarding pooling of heterogenic analysed data. The safety concerns in terms of monitoring and the failure to include associated costs for severe adverse reactions into the economic analysis have been noted. The proposed frequency for monitoring may not be sufficient to detect some of the more serious adverse drug reactions and an increased frequency of blood tests should be taken into account in the cost analysis. The proposed arguments for these concerns appear correct and reasonable. After a careful risk-benefit assessment, Alemtuzumab may still need to be considered as a treatment option for patients with highly active MS (treatment failure, side effects) before supportive care."	Comment noted. The Committee concluded that it is appropriate for the economic modelling to include the deaths observed in the trials and 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) (see section 4.16 of the FAD). The manufacturer provided narrative results of the EQ-5D-5L quality of life survey administered to people taking part in the alemtuzumab trials. The EQ-5D-5L takes into account mobility, self-care, usual activities, pain/discomfort and anxiety or depression. Comments noted. The Committee concluded that alemtuzumab could be considered a cost-effective use of NHS resources for treating adults with active relapsing–remitting multiple sclerosis and for adults with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment and adults with rapidly evolving severe relapsing-remitting multiple sclerosis (see section 4.21 and 4.22 of the FAD).

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
NHS Professional	4	"Yes, the key studies of Alemtuzumab have been identified. The limitations of the available trials and related analysis have been identified and further information has been requested accordingly. A weakness of the evidence was using only Rebiff44 in the clinical trials. Long-term safety and efficacy beyond the follow-up period remain unclear. Appropriate consideration was given to evidence related to clinical effectiveness, quality of life and economical aspects as well as clinical experts and affected patients and their families. The reason for the provisional recommendations is clear and, in view of the calculated ICER range, understandable."	Comments noted. The Committee concluded that alemtuzumab could be considered a cost-effective use of NHS resources for treating adults with active relapsing–remitting multiple sclerosis and for adults with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment and adults with rapidly evolving severe relapsing-remitting multiple sclerosis (see section 4.21 and 4.22 of the FAD).
Patient	4	As a person living with MS the primary consideration is halting/slowing disability accumulation. The longer I can remain active, tax paying, etc the least burden. Alemtuzumab represents the greatest chance of halting the relentless, frightening progression of this disease. Many with MS are willing to risk the rare serious side effects. The current 1st line treatments are relatively ineffective with regular injections and many wearing side effects. Alemtuzumab represents real hope of a permanent change to the immune system. I know of many NHS treatments that have huge negative associated costs. For example a large proportion of in-vitro fertilisation (IVF) treatments result in multiple pregnancy. This results in admissions to special care baby units, life long disability, stillbirth etc. If the years of costs for this consequence of IVF were taken into consideration this effective life changing treatment for family formation would not be available. I do not feel that a very rare serious side effect of Alemtuzumab, eg renal failure, should prevent this possibly revolutionary drug being used to huge benefit for the majority, allowing us to remain active.	Comments noted The Committee concluded that alemtuzumab could be considered a cost-effective use of NHS resources for treating adults with active relapsing–remitting multiple sclerosis and for adults with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment and adults with rapidly evolving severe relapsing-remitting multiple sclerosis (see section 4.21 and 4.22 of the FAD).

Role*	Section	Comment	Response
NHS Professional	Notes	"There is lack of transparency in paragraph 4.9. (and in the ACD as a whole) on why the Committee was not convinced of the efficacy of alemtuzumab in these subgroups based on the MTC results. The results quoted in this paragraph relate to efficacy relative to fingolimod and natalizumab but it is not explained why these results leads to a conclusion that alemtuzumab is not efficacious in these subgroups. The impact of not being able to use this medication in the highly active/rapidly evolving group will ultimately result in inevitable cns damage which would have been prevented with alemtuzumab use. This medication has a place for patients who require substantial relapse reduction to avoid irretrievable disability. There is lack of transparency in paragraph 4.9. (and in the ACD as a whole) on why the Committee was not convinced of the efficacy of alemtuzumab in these subgroups based on the MTC results. The results quoted in this paragraph relate to efficacy relative to fingolimod and natalizumab but it is not explained why these results leads to a conclusion that alemtuzumab is not efficacious in these subgroups."	Comments noted. The Committee concluded that alemtuzumab could be considered a cost-effective use of NHS resources for treating adults with active relapsing–remitting multiple sclerosis and for adults with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment and adults with rapidly evolving severe relapsing-remitting multiple sclerosis (see section 4.21 and 4.22 of the FAD).
NHS Professional	3	The EMA did not identify any issues in relation to alemtuzumab efficacy varying between highly active and non-highly active patients The EMA did not identify any issues in relation to alemtuzumab efficacy varying between highly active and non-highly active patients"	Comments noted. The Committee concluded that alemtuzumab could be considered a cost-effective use of NHS resources for treating adults with active relapsing–remitting multiple sclerosis and for adults with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment and adults with rapidly evolving severe relapsing-remitting multiple sclerosis (see section 4.21 and 4.22 of the FAD).
	4	There is lack of transparency in paragraph 4.9. (and in the ACD as a whole) on why the Committee was not convinced of the efficacy of alemtuzumab in these subgroups based on the MTC results. The results quoted in this paragraph relate to efficacy relative to fingolimod and natalizumab but it is not explained why these results leads to a conclusion that alemtuzumab is not efficacious in these subgroups.	Comments noted. The Committee concluded that alemtuzumab could be considered a cost-effective use of NHS resources for treating adults with active relapsing–remitting multiple sclerosis and for adults with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment and adults with rapidly evolving severe relapsing-remitting multiple sclerosis (see section 4.21 and 4.22 of the FAD).

Role*	Section	Comment	Response
NHS Professional	4	I do not agree with the duration of efficacy being limited to 5 years. My experience of patients is that the benefit is sustained for considerably longer. None of the patients I have treated has had a further relapse, nor progressed. Patients were included in a publication by Rice et al J Neurol 2008. It has thus proved cheaper than standard DMTs, Fingolimod or Tysabri all of which these patients would have been eligible for. There are little post treatment costs - blood testing for 5 years only, thyroxine replacement therapy for some. The infrequent infusions are much preferred by patients, whose lives are much less disrupted than the nearest equivalent available Tysabri	Comments noted. The Committee concluded that alemtuzumab could be considered a cost-effective use of NHS resources for treating adults with active relapsing–remitting multiple sclerosis and for adults with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment and adults with rapidly evolving severe relapsing-remitting multiple sclerosis (see section 4.21 and 4.22 of the FAD).
Patient	notes	'NICE' should be SHOT..... Yes, my thyroid became 'under active' through being on the Phase 3 trial, BUT this is more than compensated for by my going from relapses every 3 - 6 months, to not having any relapse for over 4 & 1/2 years. NICE's decision really, really disappoints and disgusts me. This drug has been approved by the European Medical Agency. NICE is letting everyone with RRMS down severely... Obviously no one in NICE is trying to live with the severe difficulties of living with MS. I'm horrified.....	Comments noted. The Committee concluded that alemtuzumab could be considered a cost-effective use of NHS resources for treating adults with active relapsing–remitting multiple sclerosis and for adults with highly active relapsing-remitting multiple sclerosis despite beta interferon treatment and adults with rapidly evolving severe relapsing-remitting multiple sclerosis (see section 4.21 and 4.22 of the FAD).