Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis

Appendix D

Response to consultee and commentator comments on the draft remit and draft scope

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Response to consultee and commentator comments on the provisional matrix of consultees and commentators

National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis

Response to consultee and commentator comments on the draft scope

Section	Consultees	Comments	Action
Background information	Association of British Neurologists	We do not believe it is correct to say that "SPMS is characterised by gradually more or worsening symptoms with fewer, briefer remissions and a progressive increase in disability" [there are no remissions from the progressive disability that characterises and defines SPMS]; the phrase "SPMS is characterised by more persistent or gradually progressive increase in disability" would be more accurate.	Comment noted. The background section has been updated accordingly.
	Genzyme (a Sanofi company)	We believe that the final paragraph of this section could be worded more precisely: NICE has also recommended fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults. These patients were defined as 'those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least one relapse in the previous year while on therapy, and have at least nine T2-hyperintense lesions in cranial magnetic resonance imaging (MRI) or at least one gadolinium-enhancing lesion. A "non-responder" was defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year') (NICE technology appraisal guidance 254).	Comment noted. This section is intended to give a brief description of related NICE Guidance and the recommendation for TA254 has been outlined as per the wording specified in the Guidance.
	Multiple Sclerosis Trust	Background information does not capture the impact of MS on work and family life. People with MS are commonly diagnosed between the ages of 20 and 40 and may live with MS for 30-40 years. The variable nature of MS means that people given a diagnosis of MS and their families face many years of uncertainty. The disease can have a significant impact on work and family life, both for the individual and for informal carers. Pharmacological treatment: Natalizumab is also licensed for people who continue to have relapses despite treatment with beta interferon or glatiramer	Comment noted. The scope is only intended to provide a brief overview of the condition and to define the decision problem for the appraisal. The appraisal will take into

Section	Consultees	Comments	Action
		acetate, ie it is a first line and second line treatment.	account the impact of MS on patients and their families. Natalizumab is recommended by NICE only for people with rapidly-evolving severe RRMS, and therefore it can only be considered a comparator for this group.
	United Kingdom Clinical Pharmacy Association - Neurosciences Group	For the purpose of the appraisal, we consider the information accurate and complete	Comment noted.
The technology/ intervention	Association of British Neurologists	We believe so.	Comment noted.
	Genzyme (a Sanofi company)	We would suggest the following for the technology section: “Alemtuzumab appears to selectively decrease the auto-immune reaction in 2 stages. First depleting B and T lymphyocytes through selective binding to the CD52 antigen, initiating cell lysis and reducing their circulating numbers. This is followed by a distinctive pattern of repopulation that begins within weeks and continues over time. Immunoregulatory effects of alemtuzumab could arise from alterations in the number, proportions, and properties of some lymphocyte subsets during repopulation which may indicate a rebalancing of the immune system in ways that persist beyond the actual course of treatment. These immunomodulatory effects are believed to markedly decrease inflammation and increase immune system tolerance to	Comment noted. The scope aims to give a brief description of the technology and the suggested level of detail is not required. However, further information on the administration of alemtuzumab has been included.

Section	Consultees	Comments	Action
		myelin, decreasing damage during early stages of the disease, thereby reducing disability and slowing or reversing disability progression. This is in contrast to use in B cell chronic lymphocytic leukaemia (B-CLL) where, the therapeutic objective is maximal lysis of leukemic cells (which is achieved through a higher dose and chronic dosing over 12 weeks). As such, in MS the immunomodulatory mechanism of action is believed not to suppress the body's natural defence mechanisms but permits repopulation of the immune system. Data show that there is minimal impact on the components of the innate immune system (e.g. neutrophils) which suggests that the innate immune will remain intact and able to fight infection while the adaptive immune system resets. It is administered by intravenous infusion in two annual courses of 12 mg, the first administered over 5 days, and the second course over 3 days 12 months later. After two treatments, there remains the option for further future administration at yearly intervals if a patient's clinical assessment suggests need. The Phase III extension study shows such rates of retreatment to be low at three years (18%-20%). Low rates of retreatment have also been reported up to 5 years in the extension phase of the CAMMS 223 Phase II study. Alemtuzumab does not currently have a UK marketing authorization for the treatment of RRMS. It has been studied in clinical trials as a monotherapy in comparison with high dose, high frequency subcutaneous interferon-beta (Rebif) in adults with RRMS. One trial was for treatment-naïve patients and another for those who had relapsed on previous treatment. Patients from both of these studies have been entered into extension studies and in addition results have been reported from the 5 year extension phase of the CAMMS 223 Phase II study."	
	Multiple Sclerosis Trust	The novel dosing schedule is likely to be a significant benefit and should be described in more detail (one course of iv infusions over 5 days in first year and	Comment noted. The scope aims to give a

Section	Consultees	Comments	Action
		over 3 days one year later; in most people no further treatment is necessary after these two courses of iv infusions).	brief description of the technology and details on dosing are not included. Detailed information regarding the technology, and any potential advantages from the dosing schedule, will be fully considered during the appraisal.
	Teva UK limited	The technology should be described as an immune-suppressant.	Comment noted. The mechanism of action of the technology is described sufficiently in the scope.
	United Kingdom Clinical Pharmacy Association - Neurosciences Group	For the purpose of the appraisal, we consider the information accurate.	Noted.
Population	Association of British Neurologists	In the opinion of the ABN, this assessment should certainly include [1] previously untreated RRMS patients. It should also include [2] individuals with RRMS who have proved intolerant of, or unresponsive to, previous DMT, and we believe that [3] patients with highly active and rapidly evolving RRMS should be included also. We strongly suggest, however, that these three categories of individuals with RRMS be considered separately in the assessment of the potential value and use of alemtuzumab.	Comment noted. The scope specifies that these subgroups will be considered if evidence allows. In addition, guidance will only be issued in accordance with the marketing authorisation.
	Genzyme (a Sanofi	[redacted]	Comment noted.

Section	Consultees	Comments	Action
	company)	[redacted] (proposed licence indication wording is commercial in confidence)	
	Merck Serono Ltd	In the RRMS population there is two specific subpopulations i.e. Highly active RRMS (HARRMS) and Rapidly Evolving Severe (RES) therefore the technology should consider these in the appraisal.	Comment noted. The scope specifies that these subgroups will be considered if evidence allows. In addition, guidance will only be issued in accordance with the marketing authorisation.
	MS Society and United Kingdom Multiple Sclerosis Specialist Nurse Association	The MS Society and UKMSSNA agrees with the inclusion of the sub groups listed, if the evidence allows.	Comment noted.
	Multiple Sclerosis Trust	The risk/benefit profile of alemtuzumab means that it is most likely to be licensed for people with highly active/rapidly evolving severe RRMS. Initial studies suggest it may be most effective when used early in the course of MS, so may be most appropriate as a first line rather than second line treatment. Depending on marketing authorisation, the populations likely to benefit from alemtuzumab include treatment naïve, those who have not responded to prior disease modifying treatments (DMTs), those with intolerable side effects to DMTs.	Comment noted. The scope specifies that these subgroups will be considered if evidence allows. In addition, guidance will only be issued in accordance with the marketing authorisation.
	Teva UK limited	In CARE-MS I, which compared alemtuzumab versus beta-interferon in MS patients which had received no previous MS therapy, the effect on disease progression was similar at two years in those patients receiving alemtuzumab compared to those receiving beta-interferon. CARE-MS II alemtuzumab did show reduction in relapse rate and reduction in risk of worsening disability	Comment noted. It is for the Appraisal Committee to consider the nature of the evidence available.

Section	Consultees	Comments	Action
		when compared to beta-interferon in MS patients which had experienced at least one relapse whilst taking a disease modifying therapy. As such, alemtuzumab, should only be considered as a second line therapy for those that have shown no reduction in relapse rate on standard therapies such as beta-interferon and glatiramer acetate as there is no evidence to support its use as a first line therapy	Alemtuzumab has been studied in clinical trials in the treatment-naïve population and this population cannot currently be excluded from the scope. In addition, please note that guidance will only be issued in accordance with the marketing authorisation
	United Kingdom Clinical Pharmacy Association - Neurosciences Group	The population is defined appropriately within the anticipated marketing authorisation.	Comment noted.
Comparators	Association of British Neurologists	Beta interferon and copolymer are standard treatments, but for this consideration of a novel oral therapy, we believe the recently licensed product FINGOLIMOD should also be included as a comparator. No single one of these products could be described as 'best alternative care', but in combination, one or other of these agents would always represent the best alternative for the majority of patients with RRMS. To include "best supportive care with no disease-modifying treatment" as a formal comparator would not reflect good (or defensible) clinical practice within the UK.	Comment noted. The scope includes fingolimod as a comparator for patients with highly active relapsing-remitting multiple sclerosis who have received treatment with beta interferon.
	Genzyme (a Sanofi company)	Primarily, we anticipate that alemtuzumab will be used in treatment experienced patients (use in this patient group is supported by CARE MS II study) and relevant comparators would be: Beta interferons and glatiramer acetate Specifically in relation to comparison with fingolimod, the subgroup of	Comments noted.

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		previously treated patients for which it is licensed and which is reflected in associated NICE guidance (TA 254). Fingolimod (in highly active previously treated patients in line with NICE guidance: These patients were defined as 'those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least one relapse in the previous year while on therapy, and have at least nine T2-hyperintense lesions in cranial magnetic resonance imaging (MRI) or at least one gadolinium-enhancing lesion. A "non-responder" was defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year'). This wording relates to fingolimod's licence and it is the only comparator whose use is bounded in this way. Patients with rapidly evolving severe (RES) MS (such patients may be treatment naïve or previously treated) and the comparators would be: Natalizumab (in RES in line with NICE guidance: RES is defined by two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI. Beta interferons or glatiramer acetate In addition, we anticipate that alemtuzumab would be used in treatment naïve patients (such use is supported by the CARE MS I study) and the comparators would be: Beta interferons and glatiramer acetate We will explore both our own trial data sets and data available for the comparators within the public domain to determine whether robust sub group analyses exist to support all of the comparisons listed above and which form of subgroup analysis, if any, best allows a robust comparison to be made.	
	Merck Serono Ltd	Merck Serono would like to recommend that, in keeping with NICE methodology, comparators which are used routinely in the NHS such as natalizumab and fingolimod should be included in the appraisal. For people with highly active relapsing-remitting multiple sclerosis who have an unchanged or increased relapse rate or ongoing severe relapses compared	Comments noted. The scope currently includes both technologies: natalizumab (for

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		with the previous year despite treatment with beta interferon, the comparators list should be: fingolimod, natalizumab, and best supportive care. We suggest that special consideration or distinction is given for patients with best supportive care treatment whether they received prior DMDs to those who have not. If the product is not being used exclusively in naive patients, we believe that patients have accumulated benefits from previous therapy.	patients with rapidly-evolving severe relapsing-remitting multiple sclerosis) and fingolimod (for patients with highly active relapsing-remitting multiple sclerosis who have received treatment with beta interferon).
	MS Society and United Kingdom Multiple Sclerosis Specialist Nurse Association	The treatments listed are the standard treatments used in the NHS. However, Extavia is also routinely used as a treatment for MS but sits outside the risk-sharing scheme. This treatment should be brought within the scope of the appraisal.	Comment noted. The manufacturer of Extavia is listed on the matrix as a comparator manufacturer.
	Multiple Sclerosis Trust	The MS Trust notes that best supportive care is not listed as a comparator (cf draft scope for dimethyl fumarate and teriflunomide). However the topic of best supportive care is raised under questions for consultation - our response to this is given below.	Comment noted.
	Novartis	Alemtuzumab should be considered as a comparator to fingolimod only if it receives a licence for use in patients with highly active relapsing-remitting multiple sclerosis who have previously received treatment with beta interferon.	Comment noted. Guidance will be issued only in accordance with marketing authorisation.
	Teva UK limited	In CARE-MS I, which compared alemtuzumab versus beta-interferon in MS patients which had received no previous MS therapy, the effect on disease progression was similar at two years in those patients receiving alemtuzumab compared to those receiving beta-interferon. CARE-MS II alemtuzumab did show reduction in relapse rate and reduction in risk of worsening disability when compared to beta-interferon in MS patients which had experienced at least one relapse whilst taking a disease modifying therapy. As such,	Comment noted. It is for the Appraisal Committee to consider the nature of the evidence available. Alemtuzumab has been studied in clinical trials

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		alemtuzumab, should only be considered as a second line therapy for those that have shown no reduction in relapse rate on standard therapies such as beta-interferon and glatiramer acetate as there is no evidence to support its use as a first line therapy	in the treatment-naïve population and this population cannot be excluded from the scope. In addition, please note that guidance will only be issued in accordance with the marketing authorisation
	United Kingdom Clinical Pharmacy Association - Neurosciences Group	Yes. Removal of 'best supportive care' as a comparator has been noted. This is an appropriate decision considering the controversy surrounding the term. Other novel treatments (laquinimod, dimethyl fumarate and teriflunomide) will be subject to NICE TAs post marketing authorisation and could be included.	Comment noted. The comparators include technologies that are established care in clinical practice and therefore laquinimod, dimethyl fumarate and teriflunomide cannot be included as comparators.
Outcomes	Association of British Neurologists	We believe so.	Comment noted.
	Genzyme (a Sanofi company)	Although mortality has been listed as an outcome of interest in the scope, it has not been studied as an endpoint in the alemtuzumab clinical trial programme.	Comment noted. The health-related quality of life of patients with multiple sclerosis will be captured in the quality-adjusted life year (QALY) outcome which reflects both mortality and health-related quality of life

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			effects.
	Merck Serono Ltd	Merck Serono would like to suggest that MRI outcomes should also be included in the list of outcomes measures. We feel that disability progression should only be captured by the Expanded Disability Status Scale (EDSS).	Comment noted. The inclusion of MRI outcomes was discussed in the scoping workshop. Consultees agreed that the main outcomes of importance to patients with multiple sclerosis were captured following the addition of freedom of disease activity. EDSS has been listed as an example measure for disability progression. If other types of disability status measurement instruments are used to collect disability progression, the Committee will consider their validity and robustness.
	Multiple Sclerosis Trust	Relapses have a significant impact on daily life eg work, family commitments, leisure activities. It is this aspect of relapse control which has greatest relevance to patients, rather than clinical measures. The outcome measures should reflect the wider social and economic impact of MS relapses eg days of work lost, change in employment status. Patient reported outcome measures PROMS should be included.	Comment noted. The appraisal will be conducted in accordance with the NICE methods guide which states that for the

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		There is no indication how severity of relapses would be measured. Symptoms of multiple sclerosis should reflect the list of symptoms given in the Background section. Disability progression is not included in the outcomes. Data on this outcome is being collected in current DMT clinical trials, although there has been variation in how this outcome has been measured. Also, two year trial data may not be a sufficiently long time-frame to give adequate confidence that this is a legitimate outcome for the DMTs. Freedom from disease activity is not included as an outcome but has been included in final and draft scopes for the other three DMTs being appraised. However, alemtuzumab in particular has shown potential to offer freedom from disease activity after two treatment courses. For consistency, this measure should be included in the final scope for alemtuzumab. This is a relatively new concept in DMT treatments and in response to other draft scopes we have commented that it should not be included in appraisals until there is clinical consensus on what freedom from disease activity constitutes. We also have concerns that the duration of clinical trials (1-2 years) is not sufficient to evaluate freedom from disease activity.	reference case, the perspective on outcomes should be all direct health effects, whether for patients or other people. The perspective adopted on costs should be that of the NHS and personal and social services. However, please highlight any qualitative information about the wider impact of the condition in your submission during the appraisal process. During the scoping workshop, it was agreed to include 'freedom from disease activity' as an outcome because this is becoming a more common measure for multiple sclerosis and can be evaluated from most trial data.
	Novartis	"Freedom from disease activity" has been included as a criterion in recent STAs including the final scope for DMF and should be included here for consistency	Comment noted. The scope has been updated to include this suggestion.

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	Teva UK limited	In CARE-MS I those patients receiving alemtuzumab exhibited side effect including serious thyroid disorders which were not observed in the beta-interferon group. Approximately 16-18% of alemtuzumab-treated patients in the two pivotal trials developed an autoimmune thyroid-related adverse event, and approximately 1% developed immune thrombocytopenia during. The Lead Investigator on the CARE MS I trial stated that monthly monitoring for autoimmune thyroid disease or immune thrombocytopenic will be required with alemtuzumab treatment. Although treatable, these side effects will increase the financial burden on the NHS when compared to therapies which are not associated with such side effect profiles due to increased monitoring and treatment costs.	Noted. The scope includes adverse effects of treatments as an outcome measure.
	United Kingdom Clinical Pharmacy Association - Neurosciences Group	In our opinion, yes.	Comment noted.
Economic analysis	Genzyme (a Sanofi company)	Given the long term chronic nature of MS, which impacts patient's lives from the point of diagnosis until death, the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. While we recognise that evidence that technologies result in direct health benefits for people other than patients (principally carers) can be considered within the economic evaluation as defined in section 5.2.7 of the NICE Guide to the methods of technology appraisal, we would also comment that the societal impact of MS in terms of loss of productivity, patient and carer born costs, associated disutility and ability to work etc. is much wider and not fully captured within the perspective adopted by NICE of the NHS and PSS. It should be noted that in order to include fingolimod within our health economic submission (either as a comparator or in a treatment sequence model) we will need to be made aware of its commercial in confidence discounted price agreed with NICE as part of TA 254	Comment noted. The appraisal will be conducted in accordance with the NICE methods guide which states that for the reference case, the perspective on outcomes should be all direct health effects, whether for patients or other people. The perspective adopted on costs should be that of the NHS and personal and social services. However, any

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			qualitative information about the wider impact of the condition may be included for Committee's consideration as part of your submission.
	Merck Serono Ltd	Previous NICE appraisals have not used a lifetime horizon (e.g 20 years in NICE TA32) for the base case analysis, therefore for comparability, the same time horizon should be used.	Comment noted. The scope specifies that the horizon should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.
	MS Society and United Kingdom Multiple Sclerosis Specialist Nurse Association	The statement, "costs will be considered from an NHS and Personal Social Services perspective" does not adequately address the costs to patients and carers or to society and the economy in general. MS can have a devastating impact on a person's ability to remain in employment and on the levels of informal care they require. A recent report by the Work Foundation found that 80 per cent of PwMS stop working within 15 years of the onset of diagnosis and 44 per cent retire early because of the condition (Ready to Work? Meeting the Employment and Career Aspirations of People with Multiple Sclerosis, Bevan et al, The Work Foundation, 2011). The MS Society found 82 per cent of respondents in a 2010 survey had at some point during a relapse been unable to carry out their paid employment (A submission from the MS Society to inform the NICE appraisal of fingolimod for relapsing-remitting multiple sclerosis, 2010). New evidence from a recent report by the MS Society (A lottery of treatment and care – MS services across the UK, MS Society, published as of 29 April 2013) further demonstrates the impact that MS has on the ability to remain in employment. Our report found that of those who responded to our survey only	Comment noted. The appraisal will be conducted in accordance with the NICE methods guide which states that for the reference case, the perspective on outcomes should be all direct health effects, whether for patients or other people. The perspective adopted on costs should be that of the NHS and personal and social services. However, please

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		a quarter of those of working age are in employment this compares to three-quarters of the wider UK population. Consequently the appraisal committee should take into account: - ability to remain in the workforce - stay in work or reduce absenteeism - independence for carers (The Work Foundation, 2011:4, report found that the "professional careers of 57 per cent of relatives are adversely affected by MS of a family member) - the value of informal care - the impact of informal care on carers - 87 per cent said caring for a family member or friend has had a negative impact on their mental health and 64 per cent of carers blamed their poor health on a lack of practical support and 50 per cent on not enough financial support (In Sickness and in Health, Carers Week, 2012). Our latest research shows that 71 per cent of people with MS who responded to our survey have an unpaid carer (A lottery of treatment and care – MS services across the UK, MS Society, published as of 29 April 2013). Thus the impact of caring for someone with MS should be taken into account. - reduction in social costs - increased tax revenue (Kennedy, 2009: 27) It must be taken into account that MS is frequently a chronic progressive condition that has significant impact on the quality of life of individuals with the condition and also the lives of family members.	include any qualitative information about the wider impact of disease for Committee's consideration in your submission during the appraisal process.
	Multiple Sclerosis Trust	Economic analysis does not take into account the societal costs of relapses. Relapses have a significant impact on the ability to work or undertake normal daily activities. This is likely to lead to time off work (and potentially loss of employment) both for the person with MS and informal carers, resulting in a loss of productivity.	Comment noted. The appraisal will be conducted in accordance with the NICE methods guide which states that for the reference case, the perspective on outcomes should be all

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			direct health effects, whether for patients or other people. The perspective adopted on costs should be that of the NHS and personal and social services. However, please include any qualitative information about the wider impact of disease for Committee's consideration in your submission during the appraisal process.
	United Kingdom Clinical Pharmacy Association - Neurosciences Group	no comment	Noted.
Equality	Association of British Neurologists	No age range is given in the description of 'Population(s)" relevant to this appraisal; we believe it will be necessary to be more explicit about whether the findings apply to children with RRMS (we believe children should be included).	Comment noted. Guidance will be issued in accordance with marketing authorisation.
	Genzyme (a Sanofi company)	While we recognise that evidence that technologies result in direct health benefits for people other than patients (principally carers) can be considered within the economic evaluation (see section 5.2.7 of the NICE Guide to the methods of technology appraisal), we would also comment that the societal impact of MS in terms of loss of productivity, patient and carer born costs associated disutility and ability to work etc is much wider and not fully captured within the perspective adopted by NICE of the NHS and PSS.	Comment noted. The appraisal will be conducted in accordance with the NICE methods guide which states that for the reference case, the perspective on

Section	Consultees	Comments	Action
			outcomes should be all direct health effects, whether for patients or other people. The perspective adopted on costs should be that of the NHS and personal and social services However, please include any qualitative information about the wider impact of disease in your submission for Committee's consideration.
	United Kingdom Clinical Pharmacy Association - Neurosciences Group	Potential to disadvantage patients if over the age of 50-55 (as excluded in CARE-MS I + II trials). Patients who are established on treatment before the novel products become available may still express the wish to switch (life-style, convenience, risk, adherence etc). We hope that the inequality in accessing NICE-recommended treatments (see Fingolimod) will not be repeated, otherwise patients who have been treated with glatiramer will be disadvantaged from the outset.	Comment noted. Guidance will only be issued in line with marketing authorisation, and it is not expected to be restricted to people below 50—55 years of age. The wording of NICE's recommendation for fingolimod was (and needs to be) based on the marketing authorisation for fingolimod, and this would be the same in this appraisal.

Section	Consultees	Comments	Action
Other considerations	Genzyme	We would suggest the following wording around subgroups to be considered: Treatment experienced patients with relapsing-remitting multiple sclerosis Treatment naïve patients with relapsing-remitting multiple sclerosis Specifically to allow comparison with fingolimod in line with its licence and associated NICE guidance (TA 254). Patients with highly active relapsing-remitting multiple sclerosis. These patients to be defined as 'those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least one relapse in the previous year while on therapy, and have at least nine T2-hyperintense lesions in cranial magnetic resonance imaging (MRI) or at least one gadolinium-enhancing lesion. A "non-responder" was defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year'. In line with the guidance issued for fingolimod by NICE (TA 254) Patients with rapidly evolving severe relapsing remitting multiple sclerosis. RES to be defined as two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI in line with NICE guidance issued for natalizumab (TA 127) We will explore both our own trial data sets and data for our comparators available within the public domain to determine whether robust sub group analyses exist to support all of the comparisons listed above and which form of subgroup analysis, if any, best allows a robust comparison to be made.	Comments noted. These suggestions have been incorporated into the scope.
	Merck Serono Ltd	It is currently difficult to place this potential therapy in the treatment pathway prior to the licensed indication. Despite this uncertainty and considering clinical practice in the UK plus the results of the clinical trials, if this technology is recommended by NICE we would anticipate a predominant use in the second and subsequent line setting. For the rapidly evolving severe (RES) group of patients, we believe that analyses from the clinical trials should inform if RES patients can benefit from this therapy. Furthermore, from results of the clinical trials it seems unlikely that	Comment noted.

Section	Consultees	Comments	Action
		Alemtuzumab would be use as an add-on therapy to beta-interferon or glatiramer. Regarding potential comparators not outlined by the scope, we feel that the technologies used in the third line therapy are not listed, for example mitoxantrone and methotrexate.	
	Multiple Sclerosis Trust	We are pleased that the four new DMTs (dimethyl fumarate, alemtuzumab, teriflunomide and laquinimod) are to be appraised as STAs as this will ensure timely appraisal of each of the treatments as soon as they have been licensed. The terms of the license granted to a drug will have an impact on the guidance issued by NICE. In MS, this has created de-facto patient sub-groups (eg highly active despite treatment or rapidly evolving severe) which may not reflect clinical reality or the true complexity of prescribing. There is considerable risk that this landscape could be further complicated as each of these four drugs goes through appraisal separately. First and second lines may not be easily demarcated. This could potentially be made worse by appraising the drugs singly. Opportunities to make a rational and comprehensive view of the DMTs may be lost or else have a disproportionate impact on those drugs which are appraised last. Current NICE guidance for some of the DMTs is predicated on prior treatment with one of several (but not all) of the current first line treatments. If additional drugs are approved for use in the NHS as first line treatments, this could create perverse constraints on access to 2nd or 3rd line treatments. This could potentially have a negative impact on patients for whom the most important issue is getting access to the right drug at the right time and not experiencing needless, avoidable and potentially burdensome delay. There is the prospect of increased choice but also increased complexity for patients and clinicians in weighing up the benefit and risk and making the best choice for each individual. It is crucial to do all that is possible to maximise clarity and minimise needless complexity. We would welcome consideration of the impact of any appraisals on all current NICE guidance. Clarification of the relationship between any or all of the drugs being appraised to the currently available DMTs would be welcome, including new and current sub-groups.	Comments noted. . The recommendations made by NICE in these single technology appraisals will be based on the assessment of the clinical and cost effectiveness of the technologies within their licensed indications for treating multiple sclerosis. Potential equality issues and implications of access for different patient groups will be considered by the Appraisal Committee where appropriate

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		Can NICE indicate how it proposes to manage the STA process for these new DMTs to avoid the introduction of additional constraints and ensure that those drugs licensed later are not disadvantaged? Can NICE indicate how it proposes to manage the increasing complexity of the prescribing landscape for DMTs? People who are stable on an injectable DMT should not be excluded from switching to an oral treatment if, following discussions with their neurologist, this is considered appropriate. The requirement for long-term injections places a burden on patients and can lead to reduced adherence. Self-injecting DMTs is painful, causes 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; imposes restrictions on travel. We anticipate that, given the risk/benefit profile of alemtuzumab, it is most likely to be licensed for people with highly active/rapidly evolving severe RRMS, possibly as a second line treatment. This presents a conflict between the benefits of starting alemtuzumab treatment early, to prevent the accumulation of disability due to severe relapses versus reserving alemtuzumab for second line treatment because of significant side effects. We would expect that specialist neurology centres will be initiating treatment with alemtuzumab and the risks of serious side effects discussed with the person with MS and monitored for routinely.	
	United Kingdom Clinical Pharmacy Association - Neurosciences Group	The number of available treatments for people with RRMS is on the increase which provides a wider range of DMTs. The complexity of the treatment pathway is also increasing and clear guidance in relation to current treatments and future alternatives would be helpful.	Comment noted.
Innovation	Association of British Neurologists	We believe this technology is highly innovative and does have the potential to have a major impact on the treatment of individuals with RRMS; it is a potential step change	Comment noted.
	Genzyme (a Sanofi	Alemtuzumab offers an innovation relative to other MS treatments in the mode of administration and the low rates of retreatment. It is administered by	Comment noted.

Section	Consultees	Comments	Action
	company)	intravenous infusion in two annual courses of 12 mg, the first administered over 5 days, and the second course over 3 days 12 months later. After two treatments, there remains the option for further future administration at yearly intervals if a patient's clinical assessment suggests need. The Phase III extension study shows such rates of retreatment to be low at three years (18%-20%). Low rates of retreatment have also been reported up to 5 years in the extension phase of the CAMMS 223 Phase II study. In a treatment experienced (highly active according to regulatory definition) cohort, the average EDSS score declined significantly compared to IFN over a 2 year period, conferring a reversal of accumulated disability. Alemtuzumab is the only MS drug to demonstrate a decline in average EDSS scores in clinical trials. The potential to offer a reversal of accumulated disability in this way therefore constitutes a substantial innovation relative to existing treatments. . There may be benefits for the patient associated with the use of alemtuzumab that are unlikely to be included in the QALY calculation. These arise from both the potential to avoid the burden on NHS resources and the patient of more frequently administered, chronic treatments and improved patient concordance with therapy.	
	MS Society and United Kingdom Multiple Sclerosis Specialist Nurse Association	Current treatments for highly active and rapidly evolving severe MS, fingolimod and natalizumab respectively, require daily treatment or monthly infusions. Alemtuzumab, which is likely to be used as a treatment for highly active or rapidly evolving MS, represents a major step change in that it requires an infusion just once a year for two years and in many cases no further treatment is required. This application method means that alemtuzumab meets several of the health related benefits listed by Kennedy: 1. Improvement in quality of life - enjoyment of greater dignity and independence – this treatment will give people with MS and their families and possible carers greater freedom 2. The ability to minimise the social visibility of disease or care – a yearly injection is less disruptive than infusions or injections that take place several	Comment noted.

Section	Consultees	Comments	Action
		times a week. Overall, this treatment will give people with MS a choice of a yearly injection with no further treatment required after two to three years. This would: - enable PwMS to continue everyday activities without planning their lives around their treatments and therapies - enable more independent living and improve lives of carers and families as well as PWMS - reduce stress and anxiety involved from daily or weekly injecting and overall emotional impact of injecting - added convenience and improved quality of life - lead to less dependence on family and carers - give people greater freedom particularly when planning travel. Current intravenous treatments need to be refrigerated and require administrative preparation when travelling abroad. In considering the value and innovation of a therapy that is infused typically only twice in two years, the inconvenience of injecting several times a week or going to hospital for infusions once a month and the increased dependence a friend, family member or carer must be considered by the appraisal committee as well as people's ability to take an active role in society including employment and/or taking care of their family rather than being dependent on them. This is particularly important given that MS affects women and men at stages in their lives where they will possibly have young families.	
	Multiple Sclerosis Trust	The novel dosing schedule (one course of treatment per year) may represent a significant benefit.	Comment noted.
	United Kingdom Clinical Pharmacy Association - Neurosciences Group	The technology is innovative for its short treatment course which may appeal to patients and service providers alike. There is a degree of uncertainty in terms of repeated courses after 8 days of administration.	Comment noted.
Questions for	Genzyme (a Sanofi	Has the population for alemtuzumab for treating multiple sclerosis been defined	Comments noted.

Section	Consultees	Comments	Action
consultation	company)	appropriately? Yes Have the most appropriate comparators for alemtuzumab for treating RRMS been included in the scope? Are the comparators listed routinely used in clinical practice? The comparators as routinely used in clinical practice. Primarily, we anticipate that alemtuzumab will be used in treatment experienced patients (use in this patient group is supported by CARE MS II study) and relevant comparators would be: Beta interferons and glatiramer acetate Specifically in relation to comparison with fingolimod, the subgroup of previously treated patients for which it is licensed and which is reflected in associated NICE guidance (TA 254). Fingolimod (in highly active previously treated patients in line with NICE guidance: These patients were defined as 'those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least one relapse in the previous year while on therapy, and have at least nine T2-hyperintense lesions in cranial magnetic resonance imaging (MRI) or at least one gadolinium-enhancing lesion. A "non-responder" was defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year'). This wording relates to fingolimod's licence and it is the only comparator whose use is bounded in this way. Patients with rapidly evolving severe (RES) MS (such patients may be treatment naïve or previously treated) and the comparators would be: Natalizumab (in RES in line with NICE guidance: RES is defined by two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI. Beta interferons or glatiramer acetate In addition, we anticipate that alemtuzumab would be used in treatment naïve	

Section	Consultees	Comments	Action
		patients (such use is supported by the CARE MS I study) and the comparators would be: Beta interferons and glatiramer acetate Should best supportive care be included as a comparator? No, we believe that alemtuzumab will substitute for existing treatments Are there any other subgroups of people in whom alemtuzumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? The subpopulations (treatment naïve, previously treated, treatment naïve patients with lower disease activity, treatment naïve patients with rapidly evolving severe RMRS, and previously treated patients) analyses demonstrate that the superior efficacy of alemtuzumab compared with sc INF-beta1a conferred a benefit to study patients regardless of their prior level of MS activity. NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which alemtuzumab will be licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the could have any adverse impact on people with a particular disability or disabilities. Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.	

Section	Consultees	Comments	Action
		No comment Do you consider alemtuzumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? Alemtuzumab offers an innovation relative to other MS treatments in the mode of administration and the low rates of retreatment. It is administered by intravenous infusion in two annual courses of 12 mg, the first administered over 5 days, and the second course over 3 days 12 months later. After two treatments, there remains the option for further future administration at yearly intervals if a patient's clinical assessment suggests need. The Phase III extension study shows such rates of retreatment to be low at three years (18%-20%). Low rates of retreatment have also been reported up to 5 years in the extension phase of the CAMMS 223 Phase II study. In a treatment experienced (highly active according to regulatory definition) cohort, the average EDSS score declined significantly compared to IFN over a 2 year period, conferring a reversal of accumulated disability. Alemtuzumab is the only MS drug to demonstrate a decline in average EDSS scores in clinical trials. The potential to offer a reversal of accumulated disability in this way therefore constitutes a substantial innovation relative to existing treatments. Do you consider that the use of alemtuzumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. There may be benefits for the patient associated with the use of alemtuzumab that are unlikely to be included in the QALY calculation. These arise from both the potential to avoid the burden on NHS resources and the patient of more frequently administered, chronic treatments and improved patient concordance with therapy.	

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	MS Society and United Kingdom Multiple Sclerosis Specialist Nurse Association	(1) Should best supportive care be included as a comparator? The MS Society and UKMSSNA fundamentally disagree with the use of best supportive care as a comparator for treatments for relapsing forms of MS and strongly recommends that NICE do not consider this as a comparator. Best supportive care with no disease modifying treatment is not a treatment option for relapsing forms of MS. Best supportive care is only a valid option where a patient has clear Secondary or Primary Progressive MS, without relapses or people with relapsing forms of MS who have infrequent and mild relapses such that they do not wish to be treated with a DMT. Alemtuzumab is unlikely to be indicated for either. The MS Society and UKMSSNA welcomes its exclusion from the list of comparators. This list should not be updated to include best supportive care. There is no clinical definition of what constitutes best supportive care and it is not routinely used in clinical practice for the treatment of relapsing forms of MS. A consensus statement by the MS Society, MS Trust and UKMSSNA on our view of best supportive care is attached in Appendix A.	Comment noted. Best supportive care has not been included as a comparator for alemtuzumab in this appraisal.
	Multiple Sclerosis Trust	The draft scope raises the question of best supportive care. This reflects the fact that there is no clinical definition of "best supportive care" for people with RRMS; most clinicians would assert that best supportive care for eligible patients is actually first line treatment with a DMT. Standard care with no DMT is the least desirable and least common option for managing relapsing-remitting MS (RRMS), reserved largely for when all disease modifying therapies are poorly tolerated or the person with MS has expressed a strong and enduring preference for no treatment. Research evidence supports the treatment of people with RRMS early in the disease to prevent axonal damage and irreversible disability. Current practice in the management of RRMS is active and acknowledges that even if people with MS continue to have relapses while on therapy, they may still be deriving benefit from the treatment. People with MS often have limited access to services if they are not on a DMT; those on DMTs are more likely to be seen at regular intervals by an MS	Comments noted. Best supportive care has not been included as a comparator for alemtuzumab in this appraisal.

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		neurologist and MS specialist nurse and any symptoms actively managed, resulting in reduced unplanned hospital admissions. The use of DMTs is being justified at an increasingly early stage and in pre-MS syndromes such as clinically isolated and radiologically isolated syndromes. A consensus statement representing the views of the MS Trust, MS Society and UKMSSNA on the use of best supportive care as a comparator is attached in Appendix A. There is a lack of treatment options for people who are experiencing very frequent and severe relapses that leave residual disability. Off licence treatments which are used in this population include mitoxantrone, cyclophosphamide, azathioprine, and methotrexate each of which are associated with significant side effects. We would urge the committee to consider the appraisal of alemtuzumab in the context of these alternatives.	

The Royal College of Physicians have endorsed the comments submitted to NICE by the Association of British Neurologists.

The following consultees/commentators indicated that they had no comments on the draft scope

Royal College of Nursing
Department of Health

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	*Proposal made by:*		*Action taken:* Removed/Added/Not included/Noted	*Justification:*
1.	UK MSSNA (UK MS Specialist Nurses Association)	Genzyme		Added	This group meets the inclusion criteria and has been added to the matrix.
2.	Shift MS	Genzyme			We are contacting Shift MS to find out whether they would like to take part in this appraisal.