**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal (STA)**

Alemtuzumab for the treatment of relapsing-remitting multiple sclerosis

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

**About you**

**Your name:** [redacted]

**Name of your organisation:** **Association of British Neurologists**

**Are you (tick all that apply):**

- ☑ a specialist in the treatment of people with the condition for which NICE is considering this technology?
- ☑ a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- ☑ an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

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**What is the expected place of the technology in current practice?**

How is the condition currently treated in the NHS?

**There are around 100,000 people affected with MS (PwMS) in the UK, with 30-40% having relapsing-remitting disease (RRMS) and most of the remainder having progressive forms of MS. 85% of all PwMS will initially have a relapsing remitting course. There are currently no treatments with a convincing role in altering the course of progressive MS. There are three main categories of medical treatment for people with relapsing remitting MS (pwRRMS), (i) treatment of relapses, (ii) symptomatic treatment, and (iii) disease modifying treatment (DMT). The drug discussed here (Alemtuzumab) belongs to the latter category. Current standard 1st line DMT for pwRRMS who fulfil the criteria issued by the ABN 2001 (updated 2009) consist of β-interferons and glatiramer acetate. pwRRMS who despite treatment with one of the β-interferons have on-going disease activity (either indicated by relapses and/or gadolinium-enhancing ($Gd^+$) lesions on brain magnetic resonance imaging (MRI), may switch to (2nd line) treatment with either natalizumab (monthly infusion) or fingolimod (first oral treatment licensed). Both natalizumab and fingolimod are considered by NICE as cost-effective treatments (as long as fingolimod is used within the access scheme guidelines). Natalizumab also has a NICE recommendation as a 1st line DMT in pwRRMS with a rapidly evolving severe (RES) course of their disease. Despite the availability of these more potent agents there are still a significant number of patients with treatment failure as a result of breakthrough relapses resulting in increasing disability which is likely to accrue.**

Is there significant geographical variation in current practice?

**DMT is guided by national and rather strict criteria (ABN 2001/2009 and NICE guidance, see below). Therefore, geographic variation in treatment practice should be minimal. Nevertheless, significant variation appears to exist across the UK in the interpretation of certain aspects of the mentioned guidelines, for example about the time point when to initiate treatment. A recent study by the UK MS Society revealed that pwRRMS who live in Northern Ireland are more than twice as likely to be taking DMT than if they live in Wales. Across Europe, only Poland and Romania have a smaller proportion of pwRRMS taking DMT. Uptake of these DMT appears to be driven by the availability of neurologists with expertise in MS and MS specialist nurses and their particular experience with different agents. In addition, several UK centres have been using alemtuzumab for some years, based on its availability for treating leukaemia, experience in its use, and the belief that it may fundamentally alter the natural history of MS.**

Are there differences of opinion between professionals as to what current practice should be?

**Differences in prescribing practises are based on (i) whether the 2001 or 2009* version of the ABN guidelines is being used and (ii) how strict the criteria are being applied. There is now a general tendency among colleagues to treat earlier in the course of the disease in order to try and prevent relapses thereby delaying development of disability. This means that many neurologists advocate treating with more potent therapies early in the disease course, rather than waiting to see the response to "first line", milder treatments. The problem is that the evidence on which to base practice is limited.**

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*The main difference between the two versions of the ABN guideline is the inclusion in the 2009 version of (i) patients within 12 months of a clinically significant clinically isolated syndrome when MRI evidence predicts a high likelihood of recurrent episodes (i.e. development of MS), and (ii) patients with only a single major relapse in the preceding two years, but combined with MRI evidence of continuing disease activity.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

**1st line DMT are currently all injectable drugs. These drugs (β-interferons and glatiramer acetate) reduce the frequency of relapses by about 35%. Whilst they are generally safe and well tolerated the side effects of β-interferons can be unpleasant, at least during the first 6-8 weeks of treatment (mainly flu-like symptoms & injection site reactions). Natalizumab has gained a significant foothold in the therapeutic armoury for pwRRMS in the UK, with around 3,000 people across the UK on this drug. Data from the pivotal trials suggested around 70% reduction in annualised relapse rate (ARR) compared to placebo. The major issue with natalizumab is the risk of the rare and potentially fatal infection, Progressive Multifocal Leucoencephalopathy (PML). This risk increases with exposure time (2 years is considered a cut off), JC virus antibody status and use of previous immunotherapies. There is a major issue in how to advise people who have been on natalizumab for two years or more, especially if they are JC virus positive (around 50% of the MS and general population). Fingolimod, although an oral drug, is associated with issues around first dose monitoring (due to cardiac conduction effects with a risk of significant bradyarrythmias), macular oedema, and possible infection and tumour risk, particularly herpes infections (encephalitis and disseminated zoster). It has an efficacy of around 50% reduction in ARR compared to placebo. A major difficulty in cross-trial comparison is that the control groups may behave differently in each trial, and the only way to have confidence on relative efficacy is to have head-to-head comparison studies. A further issue is the difference in ARR reduction, compared to evidence for reduced disability with treatment over time. Because of differences in the availability of DMT over time there have been differences in the patient populations compared to those recruited to the pivotal placebo controlled trials (conducted in the 1990's) . Similarly measuring disability accrual has always been controversial as the main measurement instrument (EDSS) is poor, and studies have tended to concentrate on sustained EDSS progression over two consecutive visits 3-months apart, rather than the more rigorous 6-monthly interval. As it is not uncommon for relapse symptoms to last for longer than 6-months, even this latter measurement is problematic. There is some evidence for reduction in disability progression for both natalizumab and fingolimod.**

**Two other drugs are worth mentioning in the treatment of RRMS. Azathioprine has been used in MS since the 1980s, but its side effect profile, together with relative poor efficacy mean that it is used rarely. Similarly, mitoxantrone ( used for aggressive RRMS or secondary progressive disease) is limited by cardiac toxicity (dose dependant) and leukaemia risk (approximately 1/125 patients treated), as well as practical issues in ease of use. This drug has largely been superseded by the other newer treatments mentioned.**

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

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**Our ability to stratify patients and treatments early in the disease course of relapsing remitting MS is poor. Although the disease remains very unpredictable, there are a number of features associated with poorer prognosis, including male sex, mainly motor and coordination problems early on, and more abnormalities on neurological examination. There is also good evidence that high disease activity during the first few years (≥3 relapses during the first 2 years, high lesion load on MRI at onset, $Gd^+$ lesions) predicts poor outcome, i.e. more rapid accrual of disability and early conversion to secondary progressive MS. If we could predict prognosis more accurately at the beginning of the disease, we could direct more powerful treatments where the risk/benefit equation would be in favour of greater benefit. Many neurologists are using this approach aware of the limitations of the current clinical evidence base. The rationale makes sense in clinical practice so that if the person with MS appears to have early relatively aggressive disease course, more powerful treatment should have a greater impact, potentially to the point of avoiding development of secondary progression. However, at present there is virtually no unbiased data that can be used to inform this debate. As there are no treatments to alter the course of progressive MS, and from a theoretical immunological viewpoint, earlier immunotherapy is more likely to influence the underlying process and avoid nervous system damage from MS pathology; there are strong arguments for earlier treatments in the appropriate people.**

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

**Eligibility for the drug should be evaluated by a consultant neurologist and only in specialist centres with experience in the treatment of pwMS, and follow-up provided as per standard care, i.e. every 6-12 months. The side effect profile of alemtuzumab (particularly autoimmune complications including thyroid disease, haemolytic anaemia, thrombocytopenia and renal dysfunction), necessitate regular monitoring using monthly blood tests, and appropriate action if abnormalities are found. This could theoretically be done in a shared care protocol with general practice, but the hazards and prevalence of these conditions (30%), mean that rigorous infrastructure and monitoring systems needs to be in place to avoid potentially serious consequences of system failure. Specialist administrative and nursing support is therefore required, with specialist nurses receiving the necessary training in providing advice in the use of alemtuzumab and appropriate backup from associated specialities.**

**A further issue, which applies to all of the newer treatments, is how frequently MR monitoring should occur. Many centres have adopted annual MR scanning protocols in order to detect potential complications such as PML, but also to enable more accurate monitoring of disease activity. This is standard practice for patients treated with natalizumab, the NICE approved monoclonal and should be so for an agent considered at least, and probably more, potent. Many people believe that as alemtuzumab is the most powerful treatment for MS yet available, and thus the occurrence of treatment failures (continued relapse activity) is rare, the development of new MR lesions could be an indication for further treatment. Once again, at present there is little data to support "treatment until no evidence of disease activity", but patient safety concerns are influencing clinical practice, and it is likely that**

**annual MR scanning will become a standard of care for patients with aggressive relapsing disease (the MS equivalent of thyroid function blood tests when managing thyroid disease).**

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

**The technology is being used in a small number of neurological centres, particularly those with links to Cambridge, where the drug was first used for MS in the early 1990s. As experience in its use has been combined with relatively low cost due to its license for treating leukaemia (<£3,000 total for two courses, 12 months apart), some centres have used alemtuzumab extensively. Recent publications combining the experience of UK centres in reporting the emergence of autoimmune complications has been valuable in contributing to the evidence base behind drug use.**

**The company's decision to withdraw alemtuzumab from the market, prior to re-launching after licensing has created great consternation and frustration among the UK MS community, both clinicians and patients. Fortunately, certain centres have been able to stockpile some reserves to enable continued treatment, particularly where second or further doses have been threatened by lack of availability however this may be limited by expiry dates. We understand that alemtuzumab is likely to obtain a license in Early September 2013, and recommend that it is made available to centres either in the context of a clinical trial, or to those centres with experience of using the drug until NICE makes its final decision.**

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

**The key documents to guide decisions regarding DMT in the UK are currently:**

- **NICE clinical guideline 8 (2003). Multiple sclerosis: management of multiple sclerosis in primary and secondary care. These are in the process of being revised.**
- **Revised (2009) ABN guidelines for prescribing in multiple sclerosis.**
- **NICE technology appraisal guidance 32 (2002). Beta interferon and glatiramer acetate for the treatment of multiple sclerosis.**
- **NICE technology appraisal guidance 127 (2007). Natalizumab for the treatment of adults with highly active relapsing–remitting MS.**
- **NICE technology appraisal guidance (2012). Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis.**

## The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

**Alemtuzumab is usually administered as an in-patient in two IV courses, 12 months apart. The first course is given for 5 days, preceded on the first 3 days with IV methyl prednisolone, and accompanied by anti-histamines (to minimise the associated skin rash). Twelve months later, a further 3 day course is administered. Further courses can be given if there is evidence**

**for recurrence of disease activity. Because of the risk of autoimmune complications, monthly blood monitoring is crucial to pick up the emergence of treatable diseases including thyroid disease, autoimmune thrombocytopenia or haemolytic anaemia. In practical terms, patients often find that two courses of in-patient treatment are more acceptable than monthly IV infusions (natalizumab), or frequent injections (first line treatments).**

**The potential major advantages of alemtuzumab come in terms of efficacy. Studies have used the drug within 5 years of disease onset, in people with relatively low disability scores (<3 on the 0-10 EDSS scale), who were felt to have more aggressive disease (at least two relapses in the previous 2 years, and one in the previous year). These criteria were chosen in order to increase the risk/benefit equilibrium (risks worth taking in more active disease), and in order to treat early enough to potentially alter the disease course, prior to onset of major fixed disability. This drug is a humanised monoclonal antibody targeted against CD52 on the surface of lymphocytes and monocytes. The subsequent depletion and then re-population of white cells seems to render them less immunogenic to myelin. This type of treatment is sometimes referred to as "induction" therapy, which appears to have most chance of working if used early enough. This is different to all other MS drugs, which only seem to work whilst they are being administered. Indeed, when natalizumab is stopped, there is sometimes an immune reconstitution syndrome, with disease rebound, which does not occur with alemtuzumab.**

**In terms of overall efficacy, many people believe that alemtuzumab is the most powerful of the current and emerging treatments, although there were differences between the effect sizes in phase II and III studies. Using the NICE-approved natalizumab as a comparison there was an approximately 67% reduction in relapses against placebo and a 17% vs. 29% reduction in disability. The alemtuzumab Phase II data showed a 74% reduction in ARR compared to bIFN, and significant reduction in sustained disability accumulation (9% vs. 26%). The recently published phase III data suggest relapse rate reduction by around 50% compared to bIFN, with less pronounced evidence for sustained disability reduction, again illustrating the difficulty in comparing results between trials. Early studies in MS from Cambridge, together with combined subsequent UK experience supports the lack of efficacy in more advanced forms of progressive MS, and when the disease has been present for longer periods and disability accrued as a result of progression rather than relapses. Under these conditions, the risks outweigh any potential benefits. Longer-term data is needed to confirm or deny whether early treatment prevents the onset of secondary progressive MS. Evidence for this would make a considerable difference in favour of the use of alemtuzumab.**
**At present, there is no good evidence to help predict which individuals may go on to develop autoimmune complications following alemtuzumab. There is a single centre trial investigating a treatment to use in conjunction with alemtuzumab, in order to avoid these complications.**

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.
**Whilst the starting and stopping rules of the current ABN 2009 guideline for 1st line DMT should be followed at this point in time, we are aware of discussions to modify treatment**

**strategies in the near future to systematically include MRI (and potentially other disease biomarkers) to tailor treatment more individually to achieve freedom of disease activity. The role of this drug in relation to the other NICE approved agents fingolimod and natalizumab will vary based on patient and specialist outlook and expertise. It has already been used a "rescue therapy" for patients with breakthrough disease despite therapy with natalizumab and it is likely to be widely used initially in this role. There is likely to be an adoption of this as an early (1st line) therapy in patients with aggressive disease and a poor clinical prognosis. Clearly, as with the other agents, breakthrough relapses and the presence of a significant increase in MS lesions or new enhancing lesions would suggest treatment failure. The role of each of these new agents in treating active MS is best evaluated in the context of head-to-head clinical trials. Funding for such a trial has recently been submitted to the NIHR HTA.**

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

**The initial studies and many of the subsequent trials were conducted in specialist centres in the UK. As mentioned there has already been use of this drug as rescue therapy for patients with treatment failure and early aggressive disease in many UK specialist MS centres. The studies in general reflect UK practice. In the phase III studies there was an attempt to recruit patients with aggressive disease and a likely poor prognosis but who had a relatively short disease course and who had not yet accrued considerable disability. As mentioned before, the outcomes (reduction in relapse rate and accumulation in disability as measured by a 6-month sustained increase in EDSS as opposed to less rigorous, but more commonly used 3-month sustained EDSS increase) are standard measures in Phase III disease modifying trials.**

What is the relative significance of any side effects or adverse reactions?

**As discussed, the potential side effects are not insubstantial. There is a risk of 1) Immune suppression with resultant infection (although in practice, this has not been a major problem) and 2) the induction of autoimmune disease, in particular immune thyroid disease and ITP. This requires monthly blood tests and the availability of specialist support in order to deal with these potential complications. These must be considered in the light of the potential adverse effects of the other NICE approved potent DMT including PML (natalizumab) and herpes infections (fingolimod).**

In what ways do these affect the management of the condition and the patient's quality of life?

**The QOL needs to be considered as a balance of annual infusions of a therapy with a long duration of effect (vs. monthly infusions or regular self-administered injections). The other agents also require specialist monitoring.**

Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

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**This therapy has become a standard of care for patients with treatment failure on other licensed and NICE approved therapies in many UK centres already. There is a potential tumour risk, and there have been some case reports in the literature.**

### Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.
**There have been several publications of UK experience of using alemtuzumab outside clinical trials. All of these are in the public domain.**

### Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.
**There are already centres with the infrastructure and expertise to provide this therapy. In other MS centres there will need to be a period of capacity building, in particular links with services administering biological agents and the development of systems for safe monitoring of therapy. We recommend that these treatments are best managed and concentrated in specialist centres, where expertise on the use of all DMTs can be focussed.**

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.
How would possible NICE guidance on this technology affect the delivery of care for patients with this condition?
**There is already an understanding by MS specialist neurologists and nurses of the need to treat, stratify and monitor therapeutic efficacy. There is already recognition of treatment failure and the provision of more potent therapies to these patients. The addition of this therapy will build on current practice rather than supplanting it.**

Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?
**In centres with limited experience there will be a need for education in safe administration and monitoring. There is the potential for support from existing experienced centres and also from haematology colleagues who have considerable experience in the use of this drug for haematological malignancy.**

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**Equality**
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 this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

**No**

- 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 technology;

**No**

- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

**No**

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.