

**Urgent Clinical
Commissioning Policy
Statement:
Alemtuzumab for
treating relapsing-
remitting multiple
sclerosis – third cycle
(all ages)**

NHS England Reference: 170075P



1 Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of this policy statement, we have:

- given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

In the interests of delivering an urgent interim position a rapid initial equality impact assessment has been carried out and a full equality health impact assessment will be undertaken when a clinical commissioning policy is published to replace this document.

2 Background

In May 2014 NICE published the Technology Appraisal (TA312): Alemtuzumab for treating relapsing-remitting multiple sclerosis and recommended that alemtuzumab is a treatment option, within its marketing authorisation (MA), for that indication.

The MA for alemtuzumab at the time recommended a dosage of 12 mg/day administered by intravenous infusion for two treatment courses. The initial treatment course lasts five consecutive days, followed 12 months later by the second treatment course of three consecutive days.

However, the MA also stipulated that in an open-label follow-up of alemtuzumab clinical trials, some patients received additional "as needed" treatment with alemtuzumab upon documented evidence of resumed multiple sclerosis (MS) disease activity. The additional course(s) were administered at 12 mg/day for three consecutive days (36 mg total dose) at least 12 months after the prior treatment course. If additional treatment courses are to be given they must be administered at least 12 months after the prior course.

In December 2017, the European Medicines Agency approved a revision in the licence which includes the following statement:

Up to two additional treatment courses, as needed, may be considered:

Third or fourth course: 12 mg/day on three consecutive days (36 mg total dose) administered at least 12 months after the prior treatment course in patients with MS disease activity defined by clinical or imaging features.

NHS England has started to receive requests for a third cycle of alemtuzumab.

Evidence to support this along with additional information from NICE within the published TA presented below would suggest this is a cost effective use of this medicine and may be cost saving against other options.

3 Evidence Summary

NHS England has reviewed the evidence that was considered by NICE during their original appraisal of alemtuzumab relating to TA312. It has concluded that providing a third cycle of alemtuzumab is both clinically and cost effective based on the original evidence submitted to NICE and noting the revised MA. The evidence reviewed and published by NICE in TA312 is summarised below.

Clinical trials

In the pivotal trials (detailed below) of alemtuzumab, the drug was given as two cycles, at month 0 and 12. The trials lasted three years (the phase 2 trial) and two years (the two phase 3 trials). Because of the duration of the trials it is considered that the need for re-treatment beyond the second cycle of treatment cannot be assessed.

In the extension of the phase 2 trial to extend the evidence base and duration of treatment, of the 141 patients who reached five years of follow-up, eight had required a third cycle; and of the 33 patients who reached seven years of follow-up, eight had received a third cycle (Coles 2012).

In the two phase 3 trials, formal extension studies were set up which allowed retreatment with alemtuzumab (three days of 12mg/day) if there was a single clinical relapse or two new magnetic resonance imaging (MRI) lesions. In the extension of the phase 3 trial of alemtuzumab as a first-line therapy (CARE-MSI), 393 patients were followed up to 5 years (Havdrova 2017). Of these, 110 (28%) patients received alemtuzumab retreatment: 77, 28, and 5 patients received a total of 1, 2, and 3 courses. In the extension of the phase 3 trial of alemtuzumab as a second-line therapy (CARE-MSII), 393 patients entered the extension, and 158 patients received retreatments: 113, 39 and 6 patients receiving 1, 2, or 3 additional courses, respectively, (Coles 2017).

NICE appraisal of alemtuzumab

When NICE considered the clinical and cost effectiveness evidence for alemtuzumab in this indication, they considered its use beyond a second cycle. Appraisal consultation document, NICE TA312

<https://www.nice.org.uk/guidance/ta312>, section 4.19: "The Committee discussed re-treatment with alemtuzumab. It was aware from clinical specialists that, in CARE-MS I, CARE-MS II and CAMMS233, a further cycle of alemtuzumab was offered to patients if a relapse that lasted for at least 24 hours occurred after the second annual course of infusions. It also heard from clinical specialists that further treatments were considered likely in UK clinical practice. The Committee heard from the clinical specialists that in the trials, the percentage of people who needed a third course was greater than the

percentage who needed a fourth course, and that the trend of fewer people needing successive courses lasted up to 7 years (the median follow-up time for which data were available). The Committee considered that this indicated a time-dependent rate of re-treatment, which had not been accurately reflected in the manufacturer’s model. The Committee therefore concluded that it would be more appropriate to incorporate a time-dependent rate of re-treatment in the model.” The manufacturer recalculated the models as a result of this request.

The independent health economists also factored in retreatment. In the final submission by the Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE (page 66), it highlights that: “The Genzyme Manufacturer Submission states that the majority of patients will only require two courses of treatment as the effect of alemtuzumab is assumed to persist over the long-term and so the continued benefit of alemtuzumab is modelled such that patients receive the full efficacy of alemtuzumab when they do not receive a course of treatment. As annual acquisition costs for alemtuzumab are therefore dependent on the proportion of patients who have subsequent course of treatment, in order to avoid underestimation of acquisition costs the base case assumes that 42% of patients receive a subsequent dose in year 3, based on the CAMMS 223 extension study with 0% in years 4 and 5. Beyond year 5, a 14% (42%/3) annual rate of retreatment is assumed. The ERG assessed the effect of varying this assumption on the model. Within the ERG report a further scenario was conducted where the subsequent doses in year 3 and 5+ were 60% and 20% respectively. The result of the ICER/QALY of this scenario was £8336.

The positive finding around alemtuzumab’s cost-effectiveness (that it is the most cost-effective of all licensed treatments for multiple sclerosis) is based on retreatments, including beyond year 5 through to year 20. Even taking into account retreatment beyond 2 years, alemtuzumab was deemed cost effective by the committee.

Recently, the 5 year follow up data for CARE MS I&II has been published. Combining the data from both studies, the retreatment rates for course 3 and 4 in years 3 to 5 are detailed below:

	Year 3		Year 4		Year 5	
	(n)	(%)	(n)	(%)	(n)	(%)
Course 3	143	19.3%	70	9.6%	55	7.8%
Course 4	0		45	6.2%	33	4.7%
Total retreatment rate	19.3%		15.7%		12.4%	
Total patients followed up	742		731		707	

This additional data provides further evidence that a 3rd cycle would be cost effective under the ERG model.

4 Commissioning Position

Rationale for a clinical commissioning policy statement

Third cycle alemtuzumab to treat active relapsing–remitting multiple sclerosis is of such significant clinical importance that an immediate clinical commissioning policy statement has been adopted. The time taken to develop a full clinical commissioning policy proposition for relative prioritisation and implementation would not meet the immediate need for patients, clinicians and the NHS to have clarity about whether an intervention is or is not routinely commissioned.

NHS England is receiving several requests to commence a third cycle of alemtuzumab. The alternative to agreeing a third cycle would be to switch patients to other treatment options which may be less efficacious and less cost effective.

Clinical commissioning position

Based on a limited scoping of the evidence, NHS England has concluded that there is sufficient evidence to support for the routine commissioning of this treatment for the indications and clinical criteria listed.

Clinical commissioning criteria

NHS England will fund up to three cycles of alemtuzumab as an option, within its MA, for treating adults with active relapsing–remitting multiple sclerosis.

The recommended dose of alemtuzumab is 12 mg/day administered by intravenous infusion for two initial treatment courses, with an additional treatment course if needed.

Initial treatment of two courses:

- First treatment course: 12 mg/day on 5 consecutive days (60 mg total dose)
- Second treatment course: 12 mg/day on 3 consecutive days (36 mg total dose) administered 12 months after the first treatment course.

Up to one additional treatment course, as needed, may be considered:

- Third course: 12 mg/day on 3 consecutive days (36 mg total dose) administered at least 12 months after the prior treatment course in patients with MS disease activity defined by clinical or imaging features.

Follow-up of patients:

The therapy is recommended as an initial treatment of two courses with up to one additional treatment course if needed with safety follow-up of patients from initiation of the first treatment course and until 48 months after the last infusion of the second treatment course. If an additional third course is administered, continue safety follow-up until 48 months after the last infusion.

Clinical commissioning policy development plan

It has been assessed that the development of a full policy is not needed at this time.

Should any subsequent published clinical commissioning policy be revised to 'not to routinely commission', patients started on treatment under this policy statement will continue to have access to it provided they and the clinician responsible for their care continue to believe that it is the right treatment for them.

5 Mechanism for funding

NHS England will reimburse activity undertaken within the terms of this policy statement, as follows:

- Delivery of alemtuzumab will be at providers who are currently commissioned specialised neurology centres and also within those providers where outreach clinics for MS Disease Modifying Therapies prescribing are held.
- All patients will need to be registered on NHS England's web based registration system for the third cycle. This must be done using the same reporting system as applies to all disease modifying therapies for multiple sclerosis.

6 Date of policy statement approval and review

The policy statement is effective from 17 August 2018.

A clinical commissioning policy is not planned to be developed at this stage. If a clinician, supported by peers, seeks a reappraisal by the Clinical Panel then a new 'Preliminary Policy Proposition' should be submitted. For guidance, email england.specialisedcommissioning@nhs.net.

This policy statement will be formally reviewed when NICE undertake a review of TA312.

7 References

Cohen JA, Coles AJ, Arnold, SL, et al. (2012). Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet* 2012 Nov 20 24;380(9856):1819-28.

Coles A, Brinar V, Arnold D, et al. (2012b). Efficacy and safety results from comparison of alemtuzumab and Rebif® efficacy in multiple sclerosis I (CARE-MS I): A phase 3 study in relapsing-remitting treatment-naive patients. *Neurology*. 2012;78(1).

Coles AJ, Twyman CL., Arnold, DL, et al. (2012a). Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet* 2012 Nov 24;380(9856):1829-39.

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Havrdova E, Arnold DL, Cohen JA, Hartung HP, Fox EJ, Giovannoni G, Schippling S, Selmaj KW, Traboulsee A, Compston DAS, Margolin DH, Thangavelu K, Rodriguez CE, Jody D, Hogan RJ, Xenopoulos P, Panzara MA, Coles AJ; CARE-MS I and CAMMS03409 Investigators. Alemtuzumab CARE-MS I 5-year follow-up: Durable efficacy in the absence of continuous MS therapy. *Neurology*. 2017 Sep 12;89(11):1107-1116.