NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Proposed Health Technology Appraisal

Alemtuzumab, dimethyl fumarate, laquinimod and teriflunomide for the treatment of relapsing forms of multiple sclerosis

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of alemtuzumab, dimethyl fumarate, laquinimod and teriflunomide within their licensed indications for the treatment of relapsing forms of multiple sclerosis.

Background

Multiple sclerosis (MS) is a chronic, disabling neurological disease. It occurs when the body's immune system attacks myelin, a protective sheath around nerve fibres in the brain and spinal cord. Approximately 100,000 people in the UK have MS, and about 2500 people are newly diagnosed each year.

Relapsing-remitting MS (RRMS) is one of three clinical forms of MS which affects approximately 80% of people at disease onset. It is characterised by periods of remission followed by relapses. Most people with RRMS develop secondary progressive MS (SPMS), around 65 per cent of people with RRMS will develop SPMS 15 years after being diagnosed. SPMS is characterised by gradually more or worsening symptoms with fewer, briefer remissions (or none at all) and a progressive increase in disability. MS can have a debilitating impact on quality of life, particularly during relapses, which may require hospitalisation, and be associated with significant disability and incapacity. MS has an unpredictable course with variable severity and rates of progression. Symptoms can include weakness, chronic fatigue, unsteady gait, speech problems, incontinence, visual disturbance and cognitive impairment.

There are no curative therapies available for MS. Current pharmacological management of RRMS includes the first-line use of disease modifying agents to reduce the frequency and severity of relapses. These include beta interferon and glatiramer acetate which are not currently recommended by NICE (NICE Technology Appraisal Guidance 32), but are available in the NHS through a risk-sharing scheme. For people with rapidly-evolving severe RRMS, natalizumab is recommended (NICE Technology Appraisal Guidance 127). In clinical practice, another beta interferon or glatiramer acetate or dose escalation of existing beta interferon treatment may be administered as a second-line treatment for people whose disease has had an inadequate response to their first treatment. NICE has also recommended fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults who have an unchanged or increased relapse rate or

ongoing severe relapses compared with the previous year despite treatment with beta interferon (Technology Appraisal Guidance 254).

The technologies

Alemtuzumab (Lemtrada, Genzyme, a Sanofi company) is a humanised anti-lymphocyte monoclonal antibody targeted against the CD52 surface antigen. It selectively depletes lymphocytes and monocytes that express the CD52 antigen. As well as reducing the T-cells that cause the inflammation of the myelin, it is also thought that the regenerated T-cells after treatment do not attack myelin. It is administered by intravenous infusion. Alemtuzumab does not currently have a UK marketing authorisation for the treatment of RRMS. It has been studied in clinical trials in comparison with beta-interferon in adults with RRMS.

Dimethyl fumarate (Panaclar, Biogen Idec) is a derivative of fumaric acid. It suppresses immune system molecules involved in the inflammatory response, and modulates pro-and anti-inflammatory gene expression. It is administered orally. Dimethyl fumarate does not currently have a UK marketing authorisation for the treatment of RRMS. It is being studied in clinical trials alone and in combination with either beta-interferon or glatiramer acetate compared with placebo or glatiramer acetate in adults with RRMS

Laquinimod (Brand name unknown, Teva Pharmaceuticals) is a synthetic immunomodulator which may reduce infiltration of leucocytes into the central nervous system and also may have a neuroprotective capacity. It is administered orally. Laquinimod does not currently have a UK marketing authorisation for the treatment of RRMS. It has been studied as monotherapy in clinical trials in comparison with either placebo or beta-interferon-1a in adults with RRMS.

Teriflunomide (Aubagio, Genzyme a sanofi company) is an oral, immunomodulatory, disease-modifying agent with anti-inflammatory properties. It inhibits dihydroorotate dehydrogenase which results in blocking the proliferation and functioning of activated T and B lymphocytes, which are thought to damage myelin. Teriflunomide does not currently have a UK marketing authorisation for the treatment of relapsing forms of MS. It has been studied in two clinical trials for adults with relapsing forms of MS as a monotherapy in comparison with placebo. It is also being studied in an ongoing clinical trial comparing treatment with teriflunomide with interferon beta 1-a.

Intervention(s)	For people with relapsing-remitting multiple sclerosis: • alemtuzumab • dimethyl fumarate • laquinimod • teriflunomide For people with secondary progressive multiple sclerosis who experience relapses: • teriflunomide
Population(s)	People with relapsing remitting multiple sclerosis People with secondary progressive multiple sclerosis who experience relapses
Comparators	For people with relapsing-remitting multiple sclerosis who have not been previously treated: • beta-interferon • glatiramer acetate • best supportive care with no disease-modifying treatment In addition, for people with rapidly evolving severe relapsing-remitting multiple sclerosis: • natalizumab For people with highly active relapsing-remitting multiple sclerosis who have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon: • fingolimod For people with secondary progressive multiple sclerosis who experience relapses: • beta interferon • glatiramer acetate • best supportive care with no disease-modifying treatment

Outcomes	The outcome measures to be considered include: • relapse rate • severity of relapse • disability progression • disease activity (including symptoms such as fatigue, cognition and visual disturbance) • mortality • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that 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. Costs will be considered from an NHS and Personal Social Services perspective. Arrangements within the risk-sharing scheme, which was agreed for the supply of disease modifying treatments for Multiple Sclerosis in the NHS (see Health Service Circular 2002/004), should be taken into consideration in the economic evaluation where relevant to the appraisal of these technologies.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation If the evidence allows, the following subgroups should be considered: • Patients with secondary progressive MS who experience relapses • Patients with rapidly evolving severe RRMS • Patients who have had prior treatment for MS
Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No. 254, Apr 2012, 'Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis'. Review date TBC (will be reviewed alongside TA127 and TA32).

	Technology Appraisal No. 127, Aug 2007, 'Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis'. Review date 2013. Technology Appraisal No. 32, Jan 2002, 'Multiple sclerosis – beta interferon and glatiramer acetate'. Static list. Suspended Technology Appraisal, 'Cladribine for the treatment of relapsing-remitting multiple sclerosis'. Related Guidelines: Clinical Guideline No. 8, Nov 2003, 'Management of multiple sclerosis in primary and secondary care'. Review in preparation. Earliest anticipated date of publication 2014.

Questions for consultation

Where are alemtuzumab, dimethyl fumarate, laquinimod and teriflunomide likely to be used in the current clinical pathway for the treatment of relapsing forms of multiple sclerosis?

- Will they be used as a first-line treatment, or only after initial treatment with beta-interferon or glatiramer acetate has been unsatisfactory?
- Are they likely to be used as a treatment for rapidly evolving severe relapsing-remitting MS?
- Is dimethyl fumarate likely to be used in UK clinical practice as monotherapy or as an add-on treatment to beta interferon or glatiramer acetate?
- Is teriflunomide likely to be used for the treatment of secondary progressive MS where there are still relapses?

Have the most appropriate comparators for alemtuzumab, dimethyl fumarate, laquinimod and teriflunomide for the treatment of relapsing forms of multiple sclerosis been included in the scope? Are the comparators listed routinely used in clinical practice?

Are the subgroups specified in the other considerations section of the scope considered appropriate? Are there any other subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately?

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, dimethyl fumarate, laquinimod and teriflunomide 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 technology;

- 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.

Do you consider the technologies to be innovative in their potential to make a significant and substantial impact on health-related benefits and how they might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of these technologies 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.

NICE intends to appraise these technologies through its Multiple Technology Appraisal (MTA) Process. We welcome comments on the appropriateness of appraising these technologies through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp).