Appendix A

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal

Laquinimod for treating relapsing-remitting multiple sclerosis

Draft scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of laquinimod within its licensed indication for the treatment of relapsing-remitting 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 clinical form of MS which affects approximately 80% of people at time of diagnosis. It is characterised by periods of remission followed by relapses (which may or may not result in underlying disability). Most people with RRMS will develop secondary progressive MS (SPMS). Around 65% of people with RRMS develop SPMS within 15 years of diagnosis. SMPS is characterised by gradually more or worsening symptoms with fewer, briefer remissions and a progressive increase in disability. Some people with SPMS may still experience relapses. MS has an unpredictable course with variable severity and progression. Symptoms can include weakness, chronic fatigue, unsteady gait, speech problems, incontinence, visual disturbance and cognitive impairment.

There is no cure 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 (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 a 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 RRMS in adults who have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon (NICE technology appraisal guidance 254).

The technology

Laquinimod (Nerventra, Teva Pharmaceuticals) is a synthetic immune modulator that crosses the blood brain barrier and directly modulates the central nervous system resident parenchymal cells which may reduce infiltration of leucocytes into the central nervous system. It is administered orally.

Laquinimod does not currently have a UK marketing authorisation for the treatment of RRMS. It has been studied in clinical trials in adults with RRMS as monotherapy compared with either placebo or beta interferon-1a.

Intervention(s)	Laquinimod
Population(s)	People with relapsing-remitting multiple sclerosis
Comparators	• beta-interferon • glatiramer acetate • natalizumab (for patients with rapidly-evolving severe relapsing-remitting multiple sclerosis) • fingolimod (for patients with highly active relapsing-remitting multiple sclerosis who have received treatment with beta interferon)
Outcomes	The outcome measures to be considered include: • relapse rate • severity of relapse • disability (for example, expanded disability status scale [EDSS]) • symptoms of multiple sclerosis (such as fatigue, cognition and visual disturbance) • freedom of disease activity • 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. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account. This includes the 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).
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. If the evidence allows, a subgroup of patients who have had prior treatment for MS should be considered.
Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No. 32, January 2002, 'Multiple sclerosis – beta interferon and glatiramer acetate.' Static guidance. Technology Appraisal No. 127, August 2007, 'Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis.' Review proposal date Jun 2010. Technology Appraisal No. 254, April 2012, 'Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis'. Review proposal date TBC (will be reviewed alongside TA32 and TA127). Technology Appraisal in Preparation, 'Cladribine for the treatment of relapsing-remitting multiple sclerosis.' Suspended. Technology Appraisal in Preparation, 'Alemtuzumab for treating relapsing-remitting multiple sclerosis'. Earliest anticipated date of publication TBC. Technology Appraisal in Preparation, 'Dimethyl fumarate for treating relapsing-remitting multiple sclerosis'. Earliest anticipated date of publication TBC. Technology Appraisal in Preparation, 'Teriflunomide for treating relapsing forms of multiple sclerosis'. Earliest anticipated date of publication TBC. Related Guidelines: Clinical Guideline No. 8, November 2003, 'Management

	of multiple sclerosis in primary and secondary care.' Review in preparation. Earliest anticipated date of publication 2014.

Questions for consultation

Has the population for laquinimod for treating relapsing-remitting multiple sclerosis (RRMS) been defined appropriately? In particular, is the population likely to include:

- People with previously untreated RRMS?
- People whose disease has inadequately responded to prior disease modifying therapy?
- People with highly active RRMS?
- People with rapidly evolving severe RRMS?

Have the most appropriate comparators for laquinimod for treating RRMS been included in the scope? Are the comparators listed routinely used in clinical practice?

Would any people with RRMS be treated with 'best supportive care'? If so, how should best supportive care be defined? 'Best supportive care with no disease modifying therapy'?

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 laquinimod 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 technology 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)?

Do you consider that the use of the technology 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.