RCPE
Royal College of Physicians of Edinburgh

9 Queen Street, Edinburgh, EH2 1JQ
tel: 0131 225 7324 fax: 0131 220 3939
A charity registered in Scotland, no. SC009465
Direct Dial: [redacted]
Direct Fax: [redacted]
Email: [redacted]
Fellowship Support Unit

Our Ref: JSAC/lhl

20 November 2006

Ms Laura Bridgeman
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London
WC1V 6NA

Dear Ms Bridgeman

SINGLE TECHNOLOGY APPRAISAL (STA): NATALIZUMAB FOR THE TREATMENT OF MULTIPLE SCLEROSIS - INVITATION TO SUBMIT A STATEMENT

I refer to NICE's invitation to make a statement in relation to the Single Technology Appraisal on *Natalizumab for the treatment of multiple sclerosis.* I am pleased to enclose the comments of the Royal College of Physicians of Edinburgh.

Please note that these comments have already been sent to you by e-mail.

Yours sincerely

[redacted]

[redacted] MD FRCP Edin
Secretary

Papers for Guidance Executive

Healthcare professional group/clinical specialist statement

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] **MD FRCP Edin, Secretary**

Name of your organisation (if applicable): Royal College of Physicians of Edinburgh

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.)? √ **Honorary Secretary of Medical Royal College**
- other? (please specify)

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

How is the condition currently treated in the NHS?. Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

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?

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)?

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?

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.

Throughout the world patients with relapsing remitting multiple sclerosis, and some with secondary progressive multiple sclerosis, are treated with disease modifying therapy (DMT), currently consisting of interferons ß or glatiramer acetate. The usage of these DMT, which have a modest effect, is considerably lower (about half) in the UK than in Europe and North America.

The technology under discussion has been investigated in two major clinical trials, including almost 2000 patients and nearly 4000 patient years. It is approximately twice as efficient as the currently available disease modifying therapies in terms of reducing relapse relate and delaying progression of the disease.

There is little practical information about the behaviour of sub-groups, other than by analysis of those groups in the pivotal trials. It is possible that those with more aggressive disease benefit more.

The technology should be used within specialist clinics, ideally with the same assessment system as that used during the Risk Sharing Scheme. There may be additional nursing care required to administer Natalizumab by intra-venous infusion. Eventually it could be delivered in the home environment by a community nurse.

The technology is not presently available in the UK, although there are patients throughout the UK who have been involved in the clinical trials.

There are no current clinical guidelines; the Association of British Neurologists is presently reviewing clinical guidelines in multiple sclerosis but it is improbable that it will include this new technology in the guidelines due in October/November 2006.

The suggestions being made that the technology should be used in patients who have "failed treatment with current DMT" or have what is perceived to be "aggressive disease" are not currently supported on an evidence base since neither group was involved in the pivotal trials.

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?

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.

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?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The new technology will be approximately twice as effective in the reduction of relapses and MRI scan changes, and in delaying progression of disability as currently available therapies.

In that most DMT have been shown to be most efficacious early in the course of the disease, there is no evidence to support restriction of the newest effective technology to a small group of patients.

The studies performed in Europe and North America were held under trial conditions that reflect current clinical practice and the initial use of the technology in clinical practice in North America (late 2004 to early 2005) mirrored the way in which disease modifying drugs are currently being prescribed.

The most important aspect of the novel technology is the development of progressive multi-focal leukencephalopathy (PML) in two people with multiple sclerosis, one during the course of a trial and one after the completion of the trial, and in one earlier patient treated for Crohn's disease. It seems highly likely that the combination of the ICAM 4 monoclonal antibody with other forms of immunosuppression is potentially dangerous in increasing the risk of opportunistic infection, particularly with JC virus.

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.

No additional evidence is noted.

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.

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? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

If NICE guidance recommends natalizumab for its licensed indication, delivery of MS care will significantly improve for patients. There is likely to be a need for extra staff in some centres, but many larger centres will be able to manage with existing staff. Facilities are generally already in place (IV infusion equipment etc), particularly in Risk Sharing Scheme Clinics, although more day ward space may be needed in over-stretched centres.