Multiple Sclerosis Trust
opening the door to information education and research

Response to the National Institute for Health and Clinical Excellence Appraisal Consultation Document: Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis.

Submitted by the MS Trust April 20th 2007.

In submitting these comments on the Appraisal Consultation Document we would like them to be taken in the context of our original submission in which we outlined the clinical relevance of natalizumab to people with multiple sclerosis and especially those with highly active relapsing remitting multiple sclerosis.

We are unhappy with the current recommendation by NICE and will try to list our concerns under the headings provided in your letter of March 22nd. However, in addition we wish to make a couple of general points, which are fundamental to the assessment process.

1. Sub-groups of Multiple Sclerosis are a convenience for clinical trials rather than a categorisation of separate diseases. MS was first described in 1868 and there are many aspects of the condition that remain a mystery. The sub-division of the condition into various labelled types is a recent phenomenon and reflects the need for categorisation required in clinical trials and clinical pathways, rather than the experience of someone living with the condition. In the assessment of natalizumab there is a suggestion in the Appraisal Consultation Document that highly active relapsing-remitting disease is a different disease – the MS Trust refutes this contention. People who have many relapses at the outset of their condition are simply progressing at a different rate, and their prognosis of disability is greater than that for individuals who have fewer relapses at the outset. These individuals are the most likely to benefit from aggressive treatment, and they are also the individuals for whom the risk benefit ratio is tipped by the very aggressive nature of their disease.

2. The situation with natalizumab is complicated by the fact that the original clinical trials were set up to study the drug in the full spectrum of relapsing remitting MS. The results as recognised by NICE were exceptional in comparison with the results seen with the current agents - a reduction in the annualised relapse rate of 68% and a reduction in disability progression of 54% [1]. However, in the trial where combination therapy was given (natalizumab plus beta-interferon) a risk of PML emerged. Safety analyses have been undertaken but at present we do not know whether it was the combination of the two drugs that proved dangerous or whether natalizumab alone leads to an increased risk of PML. It was for this reason, not unreasonably, that the regulatory authorities have erred on the side of caution and limited the licence indication to those people who are most at risk from their MS. NICE should not now try to over-interpret the original studies drawing conclusions from data which were intended for a very different purpose at the outset. The MS Trust asks that NICE accept that for a small group of people with MS, who have many relapses and thus a higher risk of disability, they should be given the option of being treated with the most effective licensed drug available - natalizumab.

Does the MS Trust consider that all the relevant evidence been taken into account?

The MS Trust does not consider that all the relevant evidence has been taken into account and would ask NICE to consider the following points:

- As with previous assessments of MS agents NICE has only given credence to EDSS data. Whilst the MS Trust accepts that this measure remains the mainstay of clinical trials it does not capture the multi-faceted impact of MS on the individual and their family, and it is therefore wrong to use only this assessment.
  NICE in clinical guideline number 8 "MS management in primary and secondary care" recognised the following impact of the condition:
    - weakness and cardio-respiratory impairment
    - fatigue (acute and chronic)
    - bladder problems
    - bowel problems
    - spasticity, spasms and contractures
    - ataxia (unsteadiness) and tremor
    - sensory loss
    - pain(including neuropathic pain)
    - visual loss
    - cognitive losses
    - emotionalism
    - depression and suicide
    - anxiety
    - speech difficulties
    - swallowing difficulties
    - sexual dysfunction
    - and pressure ulcers

  In a specific attempt to inform the Appraisal Committee about the full impact of MS and the positive effect of Tysabri, the MS Trust was represented at the Appraisal Committee meeting by two people with first hand knowledge. We hoped that they would be able to explain some of the effects of MS listed above, and the positive impact of natalizumab – they were not given any such opportunity. In particular they were not given time to express their views on the psychological impacts of MS, or the full impact on the life of carers. We ask NICE to remember that:
    - MS is probably the commonest single cause of cognitive loss in adults under 65 years
    - At least 50% of people with MS will be treated for depression at some stage
    - 30% of people with MS have lost their job within 2 years of diagnosis
    - Rates of suicide are 7 x 8 times higher than in age-matched controls
    - Rates of family break up and divorce are significantly increased

  It is not just that 50% of people with MS will require a walking aid or wheelchair within 10 years of diagnosis

- MS relapses are undervalued in all scientific evaluations. Relapses are not a defined event. Research has shown that an average relapse will last 55 days, but the range is significant anything from 2 days to 18 months. If several relapses occur in close succession as happens in highly active relapsing remitting MS the psychological and physical impact is devastating. The cumulative impact is greater than the individual relapses.

- No credence has been given to the risk of MS as a disease. People with MS should be allowed to balance the risk of their disease versus the potential risk of taking natalizumab.

- NICE has failed to recognise the magnitude of the QALY loss in MS. Research has now clearly shown that as a condition it is responsible for the greatest QALY loss of any condition with the exception of arthritis, which in its aggressive forms can be comparable. At high EDSS scores the relative quality of life score in MS is described as worse than death.

Does the MS Trust consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?

The MS Trust does not consider that the clinical and cost effectiveness evidence has been correctly interpreted. We ask NICE to consider the following points:

- The Committee's conclusion that best supportive care (rather than one of the currently available disease-modifying therapies) is the most appropriate comparator in this highly vulnerable group of patients demonstrates a lack of understanding of this specialist disease area. "Best supportive care" essentially means no disease-modifying therapy, and it is inconceivable that patients with the most active multiple sclerosis should receive no disease-modifying therapy at all.

- Progression of disability in patients with rapidly evolving severe multiple sclerosis is approximately twice as fast as in patients with less active multiple sclerosis. Although these patients may continue to experience clinically apparent disease activity, such as relapses, whilst on currently licensed disease-modifying therapies, this does not mean that these therapies are having no clinical benefit at all. To deny effective treatment to patients with the most active disease flies in the face of current clinical practice.

- The cost effectiveness data presented by Biogen Idec is an attempt to present an accurate model for the condition. NICE appears to challenge the population of people with MS used to collect the quality of life data as it may be biased. Clearly as the organisation that was involved in recruiting the people with MS, we would dispute this statement. The MS Trust is a non membership organisation and thus people who receive our newsletter, the vehicle for distributing the questionnaire, are there because they want to receive information about MS. We have now worked with this database on a number of projects and there is nothing to suggest that it in any way differs demographically from the overall population of people with MS. As NICE will recall the MS Trust submitted quality of life data for the original NICE assessment of the beta-interferons and the results we showed then have since been replicated in other studies both in the UK and Europe. The use of a similar database for the natalizumab work therefore seemed sensible. [One specific criticism was the response rate of 16% but it must be recognised that on the MS Trust database are families and friends of people with MS and a response rate of people with MS cannot be specifically calculated].

- Modelling of MS as a condition remains fraught with difficulty and we hope that NICE will accept that at present it is still impossible to accurately model a complex and variable condition that can run over a 40 – 50 year time frame. The natalizumab model seems to capture some improvements over earlier models, (for example people with MS can improve at stages), but it is still impossible to be certain about the reliability of any of these models. NICE should therefore accept that any cost per QALY figure generated will have a level of inaccuracy and this should be taken into account when looking at finite thresholds.

- NICE has accepted in the Appraisal Consultation Document that in the rapidly relapsing remitting group natalizumab is clinically effective. Taking on board the points above the cost effectiveness ratio is £32,000, which is within the threshold set for the current disease modifying drug therapies and at a level used in many other NICE assessments.

Does the MS Trust consider that the provisional recommendations of the Appraisal are sound and constitute a sensible basis for the preparation of guidance to the NHS?

The MS Trust does not consider that the recommendations as stated are sound. We would in particular ask NICE to reconsider their assessment on the basis that they have used the wrong comparator and this completely undermines the recommendation. People with highly active relapsing remitting MS would receive one of the current disease modifying drug therapies and to use "best supportive care" as the comparator is not an accurate reflection of good and current clinical practice.

The Appraisal Consultation Document cites NICE clinical guideline 8 Multiple Sclerosis: management of multiple sclerosis in primary and secondary care issued in 2003. Research undertaken by the Royal College of Physicians in conjunction with the MS Trust shows that little progress has been made with implementation in the NHS[2]. People with MS still need better services including access to appropriate drug therapy. The MS Trust calls upon NICE to review its current Appraisal Consultation Document to reflect the reality of multiple sclerosis, and the availability of natalizumab which is now licensed and which could make a real difference to people living with the highly active form of the condition.

1. Kappos L et al. Lancet Neurology March 2007
2. NHS Services for people with multiple sclerosis: a national survey, Royal College of Physicians. 2006 ISBN 1 86016 290 8