

## Resubmission

**natalizumab 300mg concentrate for solution for infusion  
(Tysabri<sup>®</sup>)**

**No. (329/06)**

**Biogen Idec Ltd.**

10 August 2007

The Scottish Medicines Consortium has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a resubmission

**natalizumab (Tysabri<sup>®</sup>)** is accepted for restricted use within NHS Scotland as single disease modifying therapy in highly active relapsing remitting multiple sclerosis (RRMS) only in patients with rapidly evolving severe RRMS defined by two or more disabling relapses in one year and with one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.

In a post-hoc sub-group analysis of the pivotal trial, which included patients with rapidly evolving severe RRMS, it was associated with a significant reduction in the annualised relapse rate and the probability of sustained progression of disability over two years compared with placebo.

Overleaf is the detailed advice on this product.

**Chairman,  
Scottish Medicines Consortium**

**Indication**

Natalizumab is indicated for single disease modifying therapy in highly active relapsing remitting multiple sclerosis (RRMS) for the following patient groups; patients with high disease activity despite treatment with beta-interferon and patients with rapidly evolving severe (RES) RRMS.

**Dosing information**

300mg administered by intravenous infusion every 4 weeks

**Product availability date**

July 2006

**Summary of evidence on comparative efficacy**

Natalizumab, a recombinant humanised monoclonal antibody, is a selective adhesion-molecule inhibitor and binds to the  $\alpha 4$  subunit of human integrin, which is highly expressed on the surface of all leukocytes, with the exception of neutrophils. Natalizumab is thought to act by inhibiting the migration of leukocytes into the CNS which in theory leads to a reduction of inflammation and demyelination.

One phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group study has been conducted in adults aged 18-50 years with RRMS. Patients were required to have a brain magnetic resonance imaging (MRI) scan demonstrating lesion(s) consistent with MS, at least one medically documented clinical relapse within the 12 months prior to randomisation and a baseline Expanded Disability Status Scale (EDSS) score of  $\leq 5$  (on a scale of 0 to 10, with higher scores indicative of more severe disease). Patients were excluded if they had had a relapse within 50 days prior to randomisation and/or had not stabilised from a previous relapse, or if they had received beta-interferon or glatiramer acetate for a total of six months or more, or within six months prior to screening. Patients were randomised to treatment with natalizumab 300mg (n=627) or placebo (n=315), administered intravenously every 28 days for up to 116 weeks.

The primary endpoint at one year was the reduction in rate of clinical relapse defined as new or recurrent neurological symptoms, not associated with fever or infection, lasting for at least 24 hours, and accompanied by new objective neurological findings upon examination by the Examining Neurologist at unscheduled visits. The primary endpoint at two years was the cumulative probability of sustained progression of disability at two years, defined as an increase of  $\geq 1.0$  on the EDSS from a baseline score  $\geq 1.0$  or an increase of  $\geq 1.5$  from a baseline score of 0 that was sustained for 12 weeks. A post-hoc subgroup analysis was also undertaken, at the request of the Committee for the Medicinal Products for Human Use (CHMP), in RES subjects defined by two or more disabling relapses in one year and with one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared to a previous MRI.

The mean number of relapses in the year prior to randomisation was 1.53 and 1.50 for the natalizumab and placebo groups respectively and the mean baseline EDSS score was 2.3. After one year of treatment natalizumab significantly reduced the annualised rate of relapse to 0.26 relapses per year, compared with 0.81 relapses per year for the placebo group. A sustained progression of disability over two years was significantly less likely in the natalizumab group compared with the placebo group (0.17 vs. 0.29, hazard ratio 0.58, 95% confidence interval [CI] 0.43, 0.77,  $p < 0.001$ ). The RES population comprised 148 and 61 patients in the natalizumab and placebo groups respectively. The annualised relapse rate for this sub-group analysis was 0.28 and 1.46 respectively ( $p < 0.001$ ) and the sustained progression of disability over two years was significantly less likely in the natalizumab group compared with the placebo group (hazard ratio 0.47, 95% CI 0.24, 0.93,  $p = 0.029$ ).

A second supporting study was of phase III, multi-centre parallel-group design, and recruited adults aged 18-55 years, with a diagnosis of RRMS on beta-interferon therapy for at least one year and who had had  $\geq 1$  relapse in the previous year despite beta-interferon therapy. Other inclusion and exclusion criteria and the efficacy endpoints were as described in the previous study. Patients were randomly assigned to receive natalizumab 300mg ( $n = 589$ ) or placebo ( $n = 582$ ) intravenously every four weeks in addition to interferon-beta-1a at a dose of 30micrograms intramuscularly once weekly for up to 116 weeks. At one year the annualised relapse rate was significantly improved in the beta interferon plus natalizumab group compared with the beta-interferon alone group (0.34 vs. 0.75;  $p < 0.001$ ). At two years the cumulative probability of sustained progression of disability was 0.23 and 0.29 for the beta-interferon plus natalizumab and beta-interferon alone groups, respectively ( $p = 0.02$ ).

## Summary of evidence on comparative safety

In the pivotal study the most common, clinically significant, adverse events associated with natalizumab therapy were acute hypersensitivity reactions defined as reports of hypersensitivity, allergic reaction or anaphylactic or anaphylactoid reaction by the investigator as well as any report of urticaria, allergic dermatitis or hives. These events occurred in up to 4% of patients, of which 1.3% was considered serious and 0.8% reported as anaphylactic/anaphylactoid. Hypersensitivity reactions were generally associated with the presence of anti-natalizumab antibodies. Detectable antibodies were present at some time during the study in 57 patients (9%) receiving natalizumab. Of these, 37 patients had persistent antibodies (antibodies detected at  $\geq 2$  times that were  $\geq 42$  days part) and also had an increase in infusion related adverse events and loss of efficacy of natalizumab.

Infections were generally mild to moderate in severity and occurred at a rate of around one per patient-year in each group. Serious infections occurred in 3.2% and 2.6% of patients in the natalizumab and placebo groups, respectively. In the natalizumab group the serious infections included four cases of pneumonia, and five cases of urinary tract infection or urosepsis. Following the discovery of three cases of progressive multifocal leucoencephalopathy (PML) in clinical trials (two patients with MS treated with natalizumab and beta-interferon, and one patient with Crohn's disease treated with natalizumab), an extensive safety review was undertaken. It included patients from the two phase III MS studies, a study combining natalizumab with glatiramer acetate and trials investigating natalizumab in Crohn's disease and rheumatoid arthritis. A total of 3116 patients (91%) who had received natalizumab in clinical trials (mean duration of treatment, 17.9 months) underwent evaluation for PML and no new cases were confirmed (total confirmed 1.0 per 1000 treated patients; 95% CI 0.2 to 2.8 per 1000).

## Summary of clinical effectiveness issues

The RES subgroup analysis in the pivotal trial was undertaken as the request of the CHMP and formed the basis of the licence in a RES group. However, the European Medicines agency (EMA) in the scientific discussion of the European Public Assessment Report (EPAR) noted that this subgroup analysis should be treated with caution since no documentation on the severity of relapses, either by their clinical course (leaving a neurological deficit) or by their duration, was collected through the entry criteria of the pivotal trial.

The EMA states that data from a trial in which natalizumab was given in combination with continued beta-interferon therapy are sufficient to support efficacy of natalizumab monotherapy in patients with high disease activity despite treatment with beta-interferon. They concluded that those data suggest that efficacy is mainly driven by natalizumab and not by beta-interferon since beta-interferon by definition was not sufficiently active. This assumption is open to question.

The reduction in relapse is clinically important. However, the effect it has on prevention of, or delay in, long-term disability is not clear. The mean EDSS at baseline was 2.3 and the mean increase in EDSS over 2 years was 0.04 and 0.41 for the natalizumab and placebo groups respectively. The clinical significance of a difference of 0.37 is unclear.

The EMA stated that the current safety database does not yet allow for a clear estimation of the risk of serious and/or fatal adverse events. Additionally, the summary of product characteristics for natalizumab states that as data on the safety and efficacy of natalizumab beyond two years are not available continued therapy beyond this time should be considered only following a reassessment of the potential for benefit and risk.

Natalizumab therapy should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of neurological conditions, in centres with timely access to MRI. The administration of natalizumab is by intravenous infusion in an outpatient clinic setting with resources for the management of hypersensitivity reactions. This compares with beta-interferon which is generally self-administered, at a frequency of every other day to weekly depending on the preparation.

There are no controlled comparative studies of natalizumab with existing therapies such as beta-interferon or glatiramer acetate. Inter- and intra-individual variability is large, particularly in patients with RRMS, and therefore a cautious approach should be made with respect to indirect comparisons.

Clinical experts have suggested that it would be helpful to have a 'stopping rule' for patients who have an inadequate response to natalizumab.

## Summary of comparative health economic evidence

The manufacturer submitted an economic evaluation comparing natalizumab with beta-interferon in patients with rapidly evolving symptoms (RES). The data from the sub-group analysis of the pivotal randomised controlled trial were compared with beta-interferon data from a Cochrane review; however, this was for all RRMS patients and not just for the RES sub-group. Randomised controlled trial data were extrapolated over 20 years.

The estimate of discounted net cost of natalizumab at this point in time was £34k and the discounted QALY gain was 1.36. The net cost per QALY gained was thus £25k. The manufacturer subsequently updated the costs used in the analysis and estimated a revised figure of £22,600 per QALY against beta-interferon.

There were a number of issues:

- The manufacturer only made a case for use of the treatment in rapidly evolving severe RRMS, not in sub-optimally treated.
- Data on the effectiveness of beta-interferon were taken from randomised controlled trials of its use in all patients with RRMS, not just the RES sub-group. Sensitivity analysis suggested that if the effectiveness of beta-interferon were changed to the upper limit of its 95% confidence interval this gave a cost per QALY of £28k.
- The manufacturer assumed the treatment would continue to be as effective as in randomised controlled trials while it continued to be taken, irrespective of time from start of treatment or EDSS state. However, this was varied in a sensitivity analysis and did not make a major impact on the final results because any assumption of dwindling effectiveness would apply to beta-interferon as well.

## Summary of patient and public involvement

Patient Interest Group Submission: MS Society Scotland

## Additional information: guidelines and protocols

NICE undertook a technology appraisal (number 32), of beta-interferon and glatiramer acetate for the treatment of multiple sclerosis and was published in January 2002. They concluded that a recommendation to use these medicines cannot, presently, be justified, taking both benefits and costs into account. The planned review date for this guidance was November 2004. In December 2004, NICE proposed that the review be deferred until November 2006, pending data from the Department of Health risk sharing scheme and, following consultation, NICE has decided to proceed with this proposal.

The National Collaborating Centre for Chronic Conditions, which is funded to produce guidelines for the NHS by NICE, has published a national clinical guideline for diagnosis and management of multiple sclerosis in primary and secondary care. Under the Department of Health risk sharing scheme patients with relapsing/remitting multiple sclerosis and those with secondary progressive MS in which relapse is the dominant clinical feature, who meet criteria developed by the Association of British Neurologists, are eligible for treatment with beta interferon or glatiramer acetate.

### Additional information: previous SMC advice

On 10 November 2006 following a full submission the Scottish Medicines Consortium advised:

natalizumab (Tysabri<sup>®</sup>) is not recommended for use within NHS Scotland as single disease modifying therapy in highly active relapsing remitting multiple sclerosis (RRMS) for the following patient groups; patients with high disease activity despite treatment with beta-interferon and in patients with rapidly evolving severe RRMS.

In a sub-group analysis of the pivotal trial, which included patients with rapidly evolving severe RRMS, there was a significant reduction in the annualised relapse rate in those treated with natalizumab compared with placebo. In addition, sustained progression of disability over two years was significantly less likely in patients receiving natalizumab than those receiving placebo. The economic case has not been demonstrated. The licence holder has indicated their decision to resubmit.

### Additional information: comparators

Under the Department of Health's risk-sharing scheme beta-interferon and glatiramer acetate are used in relapsing/remitting multiple sclerosis in patients satisfying pre-defined conditions.

### Cost of relevant comparators

Drug	Dose regimen	Cost per year (£) Cost per course (£)
Natalizumab	300mg by intravenous infusion once every 4 weeks	14 690*
Beta-interferon (Avonex)	30 micrograms by intramuscular injection once weekly.	8 476*
Beta-interferon (Betaferon)	250 micrograms by subcutaneous injection every other day	7 166**
Beta-interferon (Rebif)	22-44 micrograms by subcutaneous injection three times per week.	7 513 – 8 942**
Glatiramer acetate	20mg by subcutaneous injection once daily	5 824

Doses are for general comparison and do not imply therapeutic equivalence.

\* Costs from British National Formulary March 2007

\*\* Costs from Chemist and Druggist June 2007

## **Additional information: budget impact**

The manufacturer estimated the net cost of natalizumab to be £260k in year 1, rising to £1,610k in year 5. However, this included all costs and savings, including administration and treatment of MS over and above medicines costs (including therapy, GP, social work costs, etc.)

The manufacturer estimated the direct budget impact of natalizumab at £579k in year 1 based on 40 patients treated at a cost of £14,740 per patient. It was assumed that patients would otherwise be on an alternative immunomodulating drug at an estimated annual cost of £8,687 with a corresponding net drug budget impact of £232k in year 1.

By year 5 the direct budget impact would be £4.19m based on 284 patients treated with a net budget impact of £1.72m. Note that all of these figures assume:

- (i) patients would otherwise be on an alternative immunomodulating drug at an annual cost of £8,687; clinical experts state that this is not the case throughout Scotland.
- (ii) the manufacturer's estimate of patient numbers (400 in Scotland) is accurate.

Advice from clinical experts suggests that these figures may underestimate the net budget impact by as much as 100%; the number of patients eligible for treatment may be higher and the savings from displaced therapies are likely to be less.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*

*This assessment is based on data submitted by the applicant company up to and including 26 July 2007.*

*Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.*

*The undernoted references were supplied with the submission.*

Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006; 354(9):899-910.

European Medicines Agency (EMA). European public assessment report (EPAR) for TYSABRI [www.emea.eu.int](http://www.emea.eu.int)

Rudick RA, Stuart WH, Calabresi PA, Confavreux C, Galetta SL, Radue EW et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med* 2006; 354(9):911-923.

Yousry TA, Major EO, Ryschkewitsch C, Fahle G, Fischer S, Hou J et al. Evaluation of Patients Treated with Natalizumab for Progressive Multifocal Leukoencephalopathy. *N Engl J Med* 2006; 354(9):924-933.