Scottish Medicines Consortium

natalizumab 300mg concentrate for solution for infusion (Tysabri®) (No. 329/06)

Biogen Idec Ltd.

10 November 2006

The Scottish Medicines Consortium (SMC 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 full submission

natalizumab (Tysabri®) 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.

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 injection once every 4 weeks

Product availability date

14 July 2006

Summary of evidence on comparative efficacy

Natalizumab, a recombinant humanised monoclonal antibody, is a selective adhesion-molecule inhibitor and binds to the α4subunit 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 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 ≤ 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 ≥ 1.0 on the EDSS from a baseline score ≥ 1.0 or an increase of ≥ 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 ≥ 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 30µg 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 (0.38 vs. 0.81; 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). In the scientific discussion of the European Public Assessment Report (EPAR) the EMEA concluded that the data suggest that efficacy is mainly driven by natalizumab and not by beta-interferon since beta-interferon by definition was not sufficiently active. They considered the data sufficient to support efficacy in patients being treated in case of failure of beta-interferon.

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 ≥ 2 times that were ≥ 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 license in a RES group. However, the EMEA in the scientific discussion of the 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 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 EMEA 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.

Summary of comparative health economic evidence

The manufacturer compared natalizumab to beta interferon and glatiramer acetate in patients with rapidly evolving severe MS, and to beta interferon for use in prior treatment failures (PTF). The manufacturer used a twelve state Markov model (for transition to each of the 10 EDSS scores from 0 and to death) with a one year cycle time. Patients with a mean age of 30 entered the model and were treated for 20 years or until they progressed to EDSS state 7, whichever was earlier.

The clinical evidence came from an indirect comparison of data from the phase III trial of natalizumab compared to placebo and two Cochrane reviews of beta interferon and glatiramer acetate compared to placebo. Resource use and utilities for each EDSS state came from over 2,000 completed questionnaires from MS patients on the MS Trust's database. Utility values for health states over EDSS 8 were reported to be negative, that is, worse than death.

In the rapidly evolving severe group, the manufacturer reported that the incremental cost per QALY for natalizumab compared to beta interferon was £24,900; and £26,700 compared to glatiramer acetate. In the prior treatment failure group, natalizumab compared to beta interferon gave an ICER of £44,700 per QALY.

The results from the severe MS model, with beta interferon as the comparator showed the results were sensitive to changes in variables used. For example, if a 10-year time horizon was adopted, the ICER rose to £44,500. If an NHS cost perspective was used, the ICER increased to £27000 per QALY, although this estimate may still include some costs that are not NHS costs. If a different definition of sustained disease progression was used, the ICER rose to £35,700.

The economic model was developed from an existing published model and good internal and external validation information was provided. The comparators were appropriate given the current risk sharing agreement, which is under review. However, the outcome of this review could change the cost-effectiveness of natalizumab compared to either beta interferon or glatiramer acetate.

The model was very sensitive to the clinical effectiveness assumptions. The main trial was over 2 years with entry limited to those with an EDSS score of 0-5, mean 2.3. In the model, the observed treatment effect was assumed to apply to all patients up to EDSS state 7, over each of the 20 years. In addition, small changes to the definition of the model brought about large changes in the cost per QALY as evidenced by the different definition of disease progression increasing the ICER by £10,800.

Using the reported cost per QALY from an NHS perspective and adjusting for the loss in utility due to adverse events suggests the cost per QALY is around £32,000 for natalizumab compared to beta interferon and £31,000 compared to glatiramer acetate. These values, together with the considerable uncertainty around them, leads to the conclusion that the economic case for natalizumab has not been demonstrated.

Summary of patient and public involvement

Patient Interest Group: Multiple Sclerosis Society Scotland

Additional information: guidelines and protocols

NICE undertook a technology appraisal (number 32), *Beta interferon and glatiramer acetate for the treatment of multiple sclerosis* 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, however, it is to be deferred until November 2006, pending data from the Department of Health risk sharing scheme.

NICE issued guidance entitled *Multiple Sclerosis: Management of multiple sclerosis in primary and secondary care (clinical guideline 8)* in November 2003. Under the Department of Health risk sharing scheme patients with relapsing/remitting multiple sclerosis may be offered beta interferon or glatiramer acetate provided that certain conditions are met. The guideline predates the availability of natalizumab.

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.

Additional information: costs

Product	Regimen	Cost per year (£)
Natalizumab	**300mg by intravenous infusion once every 4 weeks**	**14740**†
Beta interferon (Avonex)	30 micrograms by intramuscular injection once weekly.	8502*
Beta interferon (Betaferon)	250 micrograms by subcutaneous injection every other day	7259*
Beta interferon (Rebif)	22-44 micrograms by subcutaneous injection three times per week.	7513-8942*
Glatiramer acetate	20mg by subcutaneous injection once daily	5823*

† Cost taken from company submission.
* Costs taken from the Health Service Circular 2002/004.

Doses are shown for general comparison and do <u>not</u> imply therapeutic equivalence.

Additional information: budget impact

The manufacturer estimated the gross budget impact of using natalizumab in RES and PTF patients would be £1.4M in 2006 rising to £10.6M by 2010. The corresponding net budget impact figures were £504K and £3.3M. These costs include the cost of treatment, cost of administration and cost of managing adverse events. These figures assumed that 90 patients would be treated in the first year rising to 775 by 2010.

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 30 October 2006.

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 (unless otherwise stated).

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 PUBLIC ASSESSMENT REPORT (EPAR). TYSABRI. Scientific discussion. EMEA/H/C/603, 1-38. 2006.European Medicines Agency. 1-8-2006.

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.