Economic Evaluation of Natalizumab (Tysabri) for the treatment of relapsing remitting multiple sclerosis that is rapidly evolving and severe or sub-optimally treated

National Centre for Pharmacoeconomics

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Summary

- In January 2007 Biogen Idec (Ireland) Limited submitted a cost effectiveness and budget impact analysis for the first alpha 4 integrin antagonist natalizumab in the treatment of highly active relapsing remitting multiple sclerosis for two indications i.e. rapidly evolving and severe multiple sclerosis and sub-optimally treated multiple sclerosis. The study was undertaken from the perspective of (a) the Department of Health and Children (DoHC) (b) a direct cost approach and (c) a societal approach. The base case was the societal perspective.

- The comparators used in the model were the interferon beta group of drugs and glatiramer acetate. As no head to head trials of natalizumab versus these comparators have been conducted, indirect comparisons were used to evaluate the costs and benefits of natalizumab as compared to these agents. A twelve state Markov model with a one-year time cycle was used in the cost utility analysis. The ability of natalizumab and its comparators to prevent progression to higher expanded disability status scale (EDSS) states, through prevention of disease progression was derived from clinical efficacy data. In the base case of the model the time horizon was twenty years and it was assumed that the relative risk reduction in terms of disease progression and relapse rate associated with natalizumab therapy would be maintained over this time horizon. The review group queried this assumption.

- The efficacy of natalizumab is derived from the multicentred double blind placebo controlled AFFIRM trial. In this study of 942 patients, 627 were randomly assigned to receive natalizumab (at a dose of 300mg) and 315 to receive placebo by intravenous infusion every 4-weeks for more than two years. The primary end points were the rate of clinical relapse at one year and the rate of sustained progression of disability, as measured by the EDSS, at two years. Natalizumab reduced the risk of sustained progression of disability by 42% over two years (hazard ratio 0.58; 95% confidence interval, 0.43 to 0.77; $P<0.001$). The cumulative probability of progression was 17% in the natalizumab group and 29% in the placebo group. Natalizumab reduced the rate of clinical relapse at one year by 68% ($P<0.001$) and led to an 83% reduction in the accumulation of new

or enlarging hyperintense lesions, as detected by T_2 weighted magnetic resonance imaging over two years. There were 92% fewer lesions as detected by gadolinium enhanced MRI in the natalizumab group than in the placebo group at both one and two years ($P<0.001$). In the rapidly evolving severe sub group of patients natalizumab reduced the risk of sustained progression of disability by 64% ($P=0.008$) and reduced annualised relapse rate by 81% ($P<0.001$).

- It is noted that the rapidly evolving severe subgroup of relapsing remitting multiple sclerosis included 209 patients (148 received natalizumab therapy). The documentation submitted confirms that no subgroup analysis of current disease modifying therapies in the exact populations covered by the natalizumab licence have been reported; hence it is not known whether the treatment effects observed for the current disease modifying therapies would differ in the natalizumab populations. In the base case analysis for both rapidly evolving severe and sub optimally treated multiple sclerosis comparisons, an effect size for disease modifying therapies consistent with a broad relapsing remitting multiple sclerosis population was assumed. Limitations associated with this assumption are acknowledged.

- Acute hypersensitivity reactions are the most common clinically significant adverse events associated with natalizumab therapy. Trial data indicated such events occurred in up to 4% of patients of which 1.1% were considered serious and 0.8% were reported as anaphylactic/anaphylactoid. Natalizumab is also associated with other serious adverse events including progressive multifocal leukoencephalopathy (PML). The risk of PML has been estimated at one per thousand patients treated with natalizumab for a mean of 17.9 months. In addition to PML an increased risk of other opportunistic infections with the use of natalizumab cannot be excluded. In the AFFIRM study two cases of suicidal ideation were observed in the 627 patients treated with natalizumab.

- In this cost effectiveness analysis both costs and consequences were discounted at an annual rate of 3.5%. The base case analysis (societal perspective) demonstrated natalizumab to be dominant i.e. more effective and less expensive as compared with both interferon beta and glatiramer acetate in the rapidly evolving severe (RES) subgroup. In the sub optimally treated (SOT) subgroup the incremental cost per quality adjusted life year (QALY) for natalizumab compared with interferon beta was €4,400. For the same subgroup natalizumab was dominant as compared with glatiramer acetate. Adopting a DoH&C perspective demonstrated ICER's of €30,600 and €27,100 for comparisons of natalizumab with interferon beta and glatiramer acetate, respectively in the RES sub group. The ICER's for similar comparisons in the SOT subgroup were €39,800 and €33,500.

- A series of univariate sensitivity analyses were conducted. Incorporating London/Ontario progression data, disease progression using the twelve-week definition and altering the time horizon all impacted significantly on the ICER's obtained during sensitivity analysis from a societal perspective. If the time horizon is changed from twenty to ten years the base case (societal perspective) ICER's for comparisons of natalizumab with interferon beta and glatiramer acetate increased to €11,800 and €2,400 in the RES subgroup. Similarly comparisons in the SOT subgroup increased the ICER's to €25,700 and €12,100 respectively. From the DoH&C perspective incorporating the ten-year time horizon resulted in ICER's for comparisons of natalizumab with interferon beta and glatiramer acetate of €49,200 and €51,700 in the RES subgroup. The same comparison in the SOT subgroup increased the ICER's to €61,300 and €63,800 respectively. Using the twelve-week definition of disease progression (the primary end point for the AFFIRM study) the ICER's for comparisons of natalizumab with interferon beta and glatiramer acetate increased to €38,200 and €31,900 in the RES sub group. The same comparison in the SOT subgroup increased the ICER's to €58,000 and €43,000 respectively.

- A probabilistic sensitivity analysis was conducted. The probability of acceptability at the €45,000/QALY threshold in the RES subgroup was 92.4% (natalizumab v interferon beta) and 94.8% (natalizumab v glatiramer acetate). For the SOT subgroup the probability of acceptability was 91.4% (natalizumab v interferon beta) and 91.4% (natalizumab v glatiramer acetate). The corresponding probabilities of acceptability from the DoH&C perspective were 79.8%, 83.8%, 63.5% and 71.7%. A budget impact analysis indicated that the total costs of treating patients with natalizumab would be in the region of €5.9 million in 2007 rising to over €16 million by 2011.

- From the evidence available natalizumab could be considered borderline cost effective in the Irish healthcare setting from the perspective of the DoH&C. Reimbursement may be considered on the basis that natalizumab appears cost effective from the societal perspective and that the drug could be considered a new innovative product. In view of the significant budget impact and recognised adverse effects we suggest this drug be confined initially to the hospital setting with treatment being initiated by consultant neurologists. The cost effectiveness profile may improve as the evidence base underpinning its use develops. In view of the uncertainty surrounding some of the ICERs a follow up review of the value for money associated with this product is advised.