PUBLIC SUMMARY DOCUMENT

Product: Natalizumab, concentrated solution for IV infusion, 300 mg per 15 mL, Tysabri®

Sponsor: Biogen Idec Australia Pty Ltd

Date of PBAC Consideration: November 2006

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drug) authority required listing for initial and continuing treatment, by neurologists, of clinically definite relapsing-remitting multiple sclerosis in ambulatory patients eighteen years of age or older.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

The PBAC had not previously considered this drug.

3. Registration Status

Natalizumab was registered by the TGA on 1 November 2006 for the indication:

> as monotherapy for the treatment of patients with relapsing remitting multiple sclerosis to delay the progression of physical disability and to reduce the frequency of relapse. The safety and efficacy of TYSABRI beyond two years are unknown.

4. Listing Requested and PBAC's View

Public and private hospital authority required – Section 100
Initial treatment, by neurologists, of clinically definite relapsing-remitting multiple sclerosis in ambulatory (without assistance or support) patients eighteen years of age or older. The diagnosis must be confirmed by magnetic resonance imaging (MRI) of the brain and/or spinal cord and the date of the scan included in the authority application, unless the authority application is accompanied by written certification provided by a radiologist that an MRI scan is contraindicated because of the risk of physical (not psychological) injury to the patient.

In addition, to be eligible for initial treatment, patients must *either*:
1. Have experienced at least 2 documented attacks of neurological dysfunction, believed to be due to multiple sclerosis, in the preceding 2 years, *or*:
2. Have shown progression of disability while on an existing immunomodulatory therapy (eg. interferon-beta or glatiramer acetate), and are therefore required to cease that treatment in accordance with the current PBS listing, *or*:
3. Have proven intolerant to, or unable to comply with, an existing immunomodulatory therapy, and are therefore required to cease that treatment in accordance with the current PBS listing, *or*:
4. Have developed persistent neutralising antibodies to an existing immunomodulatory treatment, as demonstrated by two consecutive negative bioactivity measurements while on treatment, which are separated by at least three months.

Authority applications must be in writing and must include:
(1) a completed authority prescription form
(2) a completed 'Natalizumab Treatment for Multiple Sclerosis Supporting Information Form' which includes the patient's date of MRI scan at which multiple sclerosis was diagnosed, and results of any relevant supporting evidence to indicate the patient meets the initial treatment criteria.
(3) a copy of the signed patient acknowledgement form that declares that the patient understands and acknowledges that PBS-subsidised treatment with natalizumab for multiple sclerosis will cease if they fail to meet the PBS-defined continuation criteria.
A maximum quantity of 6 infusions will be issued with the initial authority (1 + 5 repeats).

Continuing treatment of clinically definite relapsing-remitting multiple sclerosis in patients previously issued with an authority prescription for this drug who do not show continuing progression of disability while on treatment with this drug, and who have demonstrated compliance with, and an ability to tolerate, this therapy. Patients who have been shown to develop persistent antibodies to natalizumab, as shown by two consecutive positive anti-natalizumab antibody tests separated by at least 12 weeks, should discontinue therapy as they receive no benefit from treatment.

Authority applications must be in writing and must include:
(1) a completed authority prescription form
A maximum quantity of 3 infusions will be issued with the continuing authority (1 + 2 repeats).

See Recommendation and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

Multiple sclerosis (MS) is an incurable, degenerative disease of the brain and spinal cord, characterised by loss of areas of nerve-fibre covering (demyelination) and nerve (axonal) destruction.

Advancement in the treatment of multiple sclerosis occurred in the early and mid 1990's following the introduction of immunotherapy in the form of recombinant beta-interferons and, later, glatiramer acetate. Prior to this, the only mainstream therapies available for multiple sclerosis were oral or intravenous corticosteroids for the management of acute relapses, and a range of antispasmodics, antidepressants and other therapies for symptom management.

Natalizumab is proposed as a further disease-modifying immunotherapy agent, specifically directed at an early step in the formation of the inflammatory lesion: migration of white cells across the blood brain barrier.

6. Comparator

The submission nominated interferon beta-1b as the main comparator. The PBAC accepted this as appropriate, however noted that it would have been informative for the submission to have included a comparison to interferon beta-1a as well.

7. Clinical Trials

The submission provided an indirect comparison of natalizumab and interferon beta-1b (INFN beta-1b) using placebo as the common reference. One randomised placebo-controlled trial of natalizumab (AFFIRM trial) and one randomised placebo-controlled trial of interferon

beta-1b (IFNB MSSG trial), both conducted in patients with relapsing-remitting multiple sclerosis (RRMS), were used to conduct the indirect comparison.

The trial involving natalizumab had been published as follows:

Trial/First author	Protocol title	Publication citation
C-1801 AFFIRM		
Polman CH et al (2006)	A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis.	New England Journal of Medicine, 2006; 354: 899-910

The trial involving INFN beta-1b had been published as follows:

Trial/First author	Protocol title	Publication citation
IFNB MSSG trial		
Duquette P et al (1993)	Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial.	Neurology, 1993; 43(4 I): 655-661
Duquette P et al (1995)	Interferon beta-1b in the treatment of multiple sclerosis: Final outcome of the randomized controlled trial.	Neurology, 1995; 45(7): 1277-1285

8. Results of Trials

Key results of the indirect comparison for annualised relapse rates at one and two years for both trials were presented.

The results of the key trials are summarised in the tables below.

Results of the indirect comparison– annualised relapse rate

Trial	Rate ratio (95% CI)	Natalizumab Relapse rate (95% CI)	Placebo Relapse rate (95%CI)	INFN beta-1b Relapse rate	Rate ratio (95% CI)	Indirect estimate of effect Rate ratio (95% CI)
Results at 1 year						
AFFIRM 1 year	**0.341 (0.266, 0.436)**	N=627 0.265 (0.213, 0.330)	N= 315 0.779 (0.643, 0.944)			**0.51 (0.362, 0.722)**
IFNB MSSG 1 year			N=123 1.44 #	N=124 0.96 #	**0.67 (0.524-0.849)**	
Results at 2 years						
AFFIRM 2 years	**0.320 (0.256, 0.399)**	N=627 0.235 (0.193, 0.285)	N= 315 0.733 (0.619, 0.869)			
IFNB MSSG[C] 2 years			N=110 1.18[#]	N=107 0.85[#]	0.720 (0.535-0.969)	**0.444 (0.307, 0.643)**
			N=112 1.27	N=115 0.84	0.66 (0.455-0.961)	**0.485 (0.358, 0.657)**

Bolded font indicates statistically significant differences

[#] Rates were annualised for actual time on study (Source: 1995 published report of IFNB MSSG trial)

Although the indirect comparison suggests that natalizumab is superior in terms of relapse rate, the PBAC noted that the annualised relapse rate at one year in the placebo group in the interferon trial was around double the risk for the AFFIRM trial.

Proportion of relapse-free subjects-ITT population 2 years

Trial	Risk difference (95% CI)	Natalizumab n/N (%)	Placebo n/N (%)	INFN beta-1b n/N (%)[c]	Risk difference (95% CI)	Indirect estimate of effect ARR (95% CI)
AFFIRM 2 years	**0.26 (0.19-0.32)**	418/627 (66.7)	129/315 (41.0)			
IFNB MSSG 2 years			18/112[c] (16.1)	36/115[c] (31.3)	**0.15 (0.04, 0.26)**	0.10 (-2.2%, 23.2%)

[c] Data presented are from the 1993 published report of the IFNB MSSG trial

The proportion of patients relapse-free at 2 years, was 66.7 per cent for natalizumab as compared to 31.3 per cent for interferon. This difference was not statistically significant.

The proportion of patients who remained relapse free at 2 years in the placebo arm of the IFNB MSSG trial was 16.1% compared with 41% in the AFFIRM trial.

The PBAC considered that although both outcomes (relapse rates and proportion of relapse-free subjects), were informative, making an indirect comparison, given the difference between the placebo groups within each trial, requires the strong assumption that the effectiveness of treatment does not depend on the underlying risk of relapse in the patient population.

For PBAC's further comments on these results, *see Recommendation and Reasons*.

9. Clinical Claim

The submission claimed that natalizumab has significant advantages in effectiveness over interferon beta-1b and similar or less toxicity. The PBAC considered that while the evidence presented suggested that natalizumab may have superior efficacy in the treatment of multiple sclerosis as compared to INFN beta-1b, there were significant problems interpreting the evidence due to the use of the indirect comparison approach taken in the submission.

For PBAC's comments, *see Recommendation and Reasons*.

10. Economic Analysis

The submission presented a preliminary economic evaluation using a cost-effectiveness approach. The resources included were drug and drug administration costs. The PBAC accepted this approach as valid.

The submission estimated that the incremental cost per extra relapse avoided over one year (based on indirect comparison) would be in the range $45,000 – $55,000.

The submission estimated that the incremental cost per additional progression-free patient over two years (based on indirect comparison) would be > $200,000 (this estimate is based on an assumption in the submission that INFN beta-1b has no incremental effect on disease progression over placebo).

A modelled economic evaluation was presented. The resources included were drug costs, drug administration costs, specialist neurologist visits, other health and community care costs, (Over-The-Counter (OTC) medications, hospitalisation, hospital in the home, emergency department presentations, rehabilitation, visits to other specialist and GPs, allied therapy, equipment, home modifications, community care, personal transport, respite care, long-term care, etc.) and costs associated with relapse episodes.

The submission estimated that the base case modelled incremental cost per extra quality adjusted life year (QALY) gained over 64.4 years would be in the range $75,000 – $85,000 (this estimate is based on an assumption in the submission that INFN beta-1b has no incremental effect on disease progression over placebo).

For PBAC's comments, *see Recommendation and Reasons*.

11. Estimated PBS Usage and Financial Implications

The submission estimated that in Year 5 of listing the likely number of patients would be < 10,000 and the financial net cost to the PBS would be in the range $30 – $40 million. The PBAC considered that the estimates of usage may result in net costs ≥ $10 million/year to the PBS in the first year of listing at least.

12. Recommendation and Reasons

The PBAC agreed that the choice of comparator was appropriate but it would have been informative for the submission to have included a comparison to INFN beta-1a as well.

The PBAC considered that while the evidence presented suggested that natalizumab may have superior efficacy in the treatment of multiple sclerosis as compared to INFN beta-1b, there were significant problems interpreting the evidence due to the use of the indirect comparison approach taken in the submission. The Committee considered that patients recruited to the trials were not sufficiently comparable at baseline to support the conduct of an indirect comparison of natalizumab and INFN beta-1b, using placebo as the common reference.

Although patients in both trials were required to have a definite diagnosis of MS, the natalizumab trial (AFFIRM) enrolled patients according to the McDonald criteria which did not exist at the time the INFN beta-1b trial (IFNB MSSG) was conducted. The PBAC remained uncertain as to whether the inclusion criterion in the AFFIRM trial of at least one medically documented clinical relapse within the twelve months prior to randomisation would be comparable with the requirement in the IFNB MSSG trial for patients to have had at least two acute exacerbations during the previous two years. The PBAC noted the Pre-PBAC Response to this issue stating that 96% of patients in the AFFIRM trial had experienced two or more relapses and would have therefore satisfied the older Poser criteria. Nevertheless, the PBAC considered that the issue of comparability between the placebo groups remained uncertain and unresolved. The Committee also noted that the cost-effectiveness of treating multiple sclerosis according to the McDonald criteria has not been established in the context of PBS subsidisation.

The PBAC noted that patients in the IFNB MSSG trial appeared to have had multiple sclerosis for a longer period of time with a greater disability at baseline. The Committee also noted information on patient demographics included in the sponsor's Pre-Sub-Committee Response, providing evidence that the two populations are more comparable in terms of time since diagnosis, than originally thought. The PBAC considered however, that this did not eliminate other concerns raised in regard to differences in populations between the trials. The mean EDSS at baseline was 2.3 in AFFIRM and 2.9 in IFNB MSSG. However, the PBAC would have found it useful to know the distribution of EDSS scores at baseline in both studies to assist in understanding the clinical significance of this difference. Although this information was provided in the submission for the AFFIRM trial, baseline EDSS score distribution data are not available for the IFNB MSSG trial. The PBAC noted that the EDSS scale is non-linear over its range in comparison with the actual level of function. For example, a 1-point EDSS change at the low end of the scale reflects only a small change in function, compared to a similar change at mid-point which reflects a substantial increase in disability.

The PBAC noted that the annualized relapse rate at one year in the placebo group in the INFN trial was around double the risk in the AFFIRM trial. The PBAC considered that making an indirect comparison given this difference, requires the strong assumption that the effectiveness of treatment does not depend on the underlying risk of relapse in the patient population.

The PBAC also noted that the IFNB MSSG trial was conducted more than a decade earlier than the AFFIRM trial, and there may be reasons to believe that management of RRMS could have changed in the time between the trials in ways that are likely to affect some of the trial outcomes, for example management of relapses and the consequent impacts on progression of

disability. The PBAC noted the sponsor's comment on this issue in it Pre-Sub-Committee Response, however considered that this was not adequately addressed in the submission.

The PBAC agreed that the indirect comparison suggested that natalizumab is superior in terms of relapse rate, however noted that the magnitude of this superiority is dependent on the effect measure used. The PBAC noted the proportion of patients relapse-free at 2 years, with the difference between the trials not being statistically significant.

The PBAC noted the Pre-PBAC Response concern regarding the focus on the secondary outcome of proportion of patients relapse free at one year 'at the expense of" the primary outcome of the annualised relapse rate, because the former loses information on how many relapses a patient may have in a year. The PBAC considered that both outcomes were informative in the context of an indirect comparison in which concerns were raised about the comparability of the patients enrolled in the trials.

The PBAC noted the risk of developing progressive multifocal leukoencephalopathy (PML) with natalizumab treatment. This risk is stated to be around 1 in 1000, but if it occurs is highly likely to cause death or severe disability. Given the seriousness of this adverse event, the Committee agreed that any restriction should include a Cautionary NOTE and specify that treatment is restricted to monotherapy, as this is thought to limit the risk of developing PML. The PBAC noted that the TGA registered indication includes a statement that the safety and efficacy of natalizumab beyond two years is unknown and that this should also be included in any PBS restriction for natalizumab. The PBAC endorsed the prescribing education program proposed by the sponsor noting that this was a condition of registration.

In regard to the requested restriction, the PBAC considered that the inclusion of criteria 2 and 3 of the initial treatment restriction is not appropriate as they imply that natalizumab should be used as second line therapy to interferon beta. The requested restriction therefore did not match the patient population included in the AFFIRM study, as almost all patients in the trial were treatment naïve, and the submission's proposed restriction would unnecessarily dictate clinical practice in an area where a standard treatment algorithm has not been established.

The PBAC had concerns about the economic evaluation and considered overall that the incremental cost-effectiveness ratio to be high at $75,000-$85,000 per QALY compared with INFN beta-1b, uncertain and likely to be biased in favour of natalizumab.

The Committee was concerned that the economic model did not adequately reflect the treatment pathways, disease progression or resource utilisation of patients in the PBS setting. The question of whether the utilities were applied appropriately also contributed to the uncertainty.

The PBAC considered that the structure of the model did not adequately represent the natural history of multiple sclerosis. Firstly, there are differences in the transitions assumed possible for patients having disease progression and 'on treatment' and patients having disease progression and 'off treatment'. Secondly, the model assumed that patients discontinuing treatment will not commence treatment with other available therapies, which is not substantiated in the submission. Thirdly the model did not include health states that account for natalizumab-treated patients discontinuing therapy because they develop neutralising antibodies, but who do not have progression of disability. The Committee was also

concerned that the discontinuation rule assumed by the model did not adequately reflect the interpretation of the requested restriction.

The PBAC was concerned about the utilities derived from Fisk et al and whether the submission adequately justifies the utilities assumed in the model. It noted the Pre-Sub-Committee Response that the precise utility weights were sourced from the author, however the utility of health states in the model were estimated by taking the average of the EDSS scores and the submission did not provide sufficient detail to enable independent verification of results. Resource utilisation by disability level was based on a small unpublished study with a sample size of only thirty in an Australian setting while the costs of managing a relapse episode was based on a US study, which raised concerns about differences in practices between the two countries.

The PBAC noted that the submission relies on the fact that there is a non-significant difference in disease progression in the IFNB MSSG trial between INFN beta-1b and placebo, as a basis to use only the results of the AFFIRM trial to estimate the benefit of natalizumab over IFNB beta 1b. The PBAC acknowledged the argument presented by the Pre-PBAC Response that the ESC estimate of a cost per progression free patient over two years of approximately $1,000,000 based on no difference in progression between nataluzimab and IFNB beta 1b was extreme. However, the Committee felt that this does not negate the fact that the comparison presented in the submission favoured natalizumab. Hence the estimated cost-effectiveness ratio of $75,000-$85,000 per QALY is the best case for natalizumab. This estimate is carried into the modelled economic evaluation, and hence the cost per QALY favoured natalizumab, accordingly.

Overall, the PBAC acknowledged that natalizumab represents the first additional effective treatment option in several years for this distressing disease and agrees that the submission demonstrates a clinical benefit. However, notwithstanding this, the Committee considered that the optimistic estimated base case cost-effectiveness ratio of $75,000-$85,000 per QALY to be high and uncertain, and rejected the submission on this basis.

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Due to the clear clinical need for new therapeutic options in the management of multiple sclerosis, the sponsor will work with the PBAC with a view to ensuring access to TYSABRI through the PBS for this incurable, debilitating disease.