# Neurological Subcommittee of PTAC
# Meeting held 27 July 2012

# (minutes for web publishing)

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Note that this document is not necessarily a complete record of the Neurological Subcommittee meeting; only the relevant portions of the minutes relating to Neurological Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

The Neurological Subcommittee may:

(a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or
(c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

These Subcommittee minutes were reviewed by PTAC at its meeting on 8 & 9 November 2012, the record of which will be available in January 2013.

## 2 Therapeutic Group Review

2.1 The Subcommittee noted the minutes from PTAC and the Analgesic Subcommittee's review of an application to fund pregabalin for neuropathic pain. The Subcommittee considered that pregabalin appeared to offer few clinical benefits over gabapentin and that the relative costs are likely to be a factor in determining funding and treatment sequencing.

2.2 The Subcommittee noted the use of rizatriptan has grown quickly since listed in 2008. The Subcommittee considered that there may be an unmet need for an oral 5-HT agonist with fast onset of action to provide an alternative to sumatriptan injections. The Subcommittee noted that naratriptan has a slower absorption rate than oral sumatriptan and therefore is unlikely to be considered. The Subcommittee **recommended** that PHARMAC staff conduct a comparison of all available 5-HT agonists, particularly focussing on the rate of onset of action between products for review by the Subcommittee at the next meeting.

*Schedule amendments*

2.3 The Subcommittee considered that two products, clonazepam and clonidine should be reclassified due to the small usage in their current therapeutic subgroups. The Subcommittee considered that the usage of clonazepam as an anti-epilepsy agent is likely to be low and **recommended** that it be reclassified to the Anxiolytic subgroup of the Schedule. The Subcommittee considered that clonidine is rarely used for migraine prophylaxis and therefore should only be listed in the Cardiovascular therapeutic group.

## 3 Fingolimod

### Application

3.1 The Subcommittee considered a funding application from Novartis for fingolimod (Gilenya) for the treatment of relapse remitting multiple sclerosis.

### Recommendation

3.2 The Subcommittee **recommended** that fingolimod be funded with a medium priority for patients who have a stable or increasing relapse rate compared with the relapse rate on starting treatment despite at least 6 months treatment with either beta interferon or glatiramer, noting that this treatment sequencing would be difficult within the current Special Authority criteria.

The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals.*

### Discussion

3.3 The Subcommittee considered the evidence provided in support of the application in particular the two pivotal trials comparing the safety and efficacy of fingolimod with placebo (FREEDOMS reported by Kappos et al. N Eng J Med 2010; 362: 387-401) and with Avonex (TRANSFORMS reported by reported by Cohen et al. N Engl J Med 2010).

3.4 The Subcommittee noted that compared with placebo, 0.5 mg fingolimod daily reduced relapses over 2 years, with the annual relapse rate of 0.18 fingolimod vs 0.40 placebo ($p<0.001$) and the hazard ratio for disability progression over 3 months was 0.7 ($p=0.02$) as reported in FREEDOMS. The Subcommittee noted that the effect of treatment on progression was measured over a very short period of time and can not necessarily be extrapolated, therefore longer term studies are required to establish this.

3.5 The Subcommittee considered the TRANSFORMS trial reported by Cohen et al. (N Engl J Med 2010; 362:402-15), which was a one year multicentre, randomised, double-blind, double dummy, parallel group phase III study. 1,281 patients with relapse remitting MS were randomly assigned (1:1:1) to 12 months treatment with once daily fingolimod 0.5 mg or 1.25 mg capsules, or interferon beta-1-alpha (Avonex) 30 ug weekly. The Subcommittee considered that compared with 30 ug weekly interferon beta-1-alpha (Avonex), fingolimod 0.5 mg daily was superior in reducing relapses. The annual relapse rate for fingolimod was 0.16 compared with 0.33 (p,0.001) for Avonex. The Subcommittee considered that reporting of disease worsening in TRANSFORMS was unclear and therefore it would be difficult to use this data to estimate the effect of fingolimod on progression.

3.6 The Subcommittee noted that EDSS progression is non-linear and therefore it is difficult to extrapolate the effects of treatment on patients beyond the study. The Subcommittee noted however, that based on previous evidence reviewed (Naci et al. J Med Econ 2010;13:78-89), there appears to be a good relationship between EDSS and quality of life (QOL), therefore studies which report QOL can be useful.

3.7 The Subcommittee considered that patients who used 1.25 mg fingolimod in the studies reported a greater incidence of side effects when compared with fingolimod 0.5 mg. The Subcommittee considered that there is some uncertainty about the safety of fingolimod given the short duration of the studies, and long-term data would provide greater certainty. The Subcommittee noted that the most common serious side effects reported in the trials were macular oedema and first dose bradycardia, varicella zoster, and there is possibly an increased risk of lymphoid malignancy.

3.8 The Subcommittee considered that fingolimod should be used as monotherapy, after patients had used an adequate course of either beta-interferon or glatiramer or both and had continued to deteriorate, noting that these first line treatments have more long term safety data. However, the Subcommittee considered that the use of fingolimod later in the course of disease (>EDSS 4.0) is likely to have fewer benefits than if used earlier. The Subcommittee considered that preventing relapses in the early stages of MS, (before EDSS 3.0 to 4.0) appears to have an effect on disease worsening (Scalfari et al. Brain 2010: 113; 1914-1929).

3.9 The Subcommittee considered that treatment switching is likely to be more effective if an alternative product with a different mode of action is used. the Subcommittee noted that a wash out period of 2 months would be used between first line treatments and fingolimod.

3.10 The Subcommittee considered that the use of fingolimod would be associated with a number of additional health sector costs including screening for pre-existing macular disease, first dose observation (bradycardia) and on-going annual ophthalmology,

dermatology and serology reviews. The Subcommittee considered that a varicella zoster vaccine could be considered prior to fingolimod treatment.

3.11 The Subcommittee noted that the supplier's cost-effectiveness assumptions had been based on the Roskell meta-analysis of disease progression, used in the supplier's analysis. The Subcommittee noted that it is unclear how the result had been calculated but seemed plausible provided that the methodology is sound.

## 4 Natalizumab

### Application

4.1 The Committee considered a funding application from Biogen Idec for natalizumab (Tysabri) for the treatment of relapsing remitting multiple sclerosis (RRMS).

### Recommendation

4.2 The Subcommittee **recommended** that natalizumab be funded with a high priority for patients who have a stable or increasing relapse rate compared with the relapse rate on starting treatment despite at least 6 months treatment with either beta interferon or glatiramer, noting that this treatment sequencing would be difficult within the current Special Authority criteria..

The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

### Discussion

4.3 The Subcommittee considered the pivotal study in the development of natalizumab as reported by Polman et al (N Engl J Med 2006; 354:899-910), AFFIRM, a two year phase three trial of natalizumab 300 mg once every 4 weeks vs placebo for up to 116 weeks in 942 patients with relapsing multiple sclerosis. The authors reported that natalizumab reduced the risk of sustained progression of disability by 42% over two years (hazard ratio, 0.58; 95% CI, 0.43 to 0.77, p<0.001) and the cumulative probability of progression (on the basis of Kaplan–Meier analysis) was 17% in the natalizumab group and 29% in the placebo group. After one year of treatment, the annualised rate of relapse was 0.26 relapse per year compared with 0.81 relapse per year in the placebo group (P<0.001).

4.4 The Subcommittee considered a number of indirect comparisons provided in the application to estimate the effect of natalizumab in comparison to beta interferon, glatiramer and fingolimod. The Subcommittee noted that there appears to be some reduction in relapse relative to the "ABC" therapies reaching statistical significance in the indirect comparison; delay of disease progression numerically favouring natalizumab over "ABC" therapies although this advantage did not reach statistical significance in the indirect comparison.

4.5 The Subcommittee considered the strength and quality of the evidence to be good. The Subcommittee considered that natalizumab has a unique mode of action compared with currently funded treatments which is a benefit.

4.6 The Subcommittee considered that natalizumab would be used as monotherapy, after patients had used an adequate course of either beta-interferon or glatiramer or both and had continued to deteriorate, noting that these first line treatments have more long term safety data. The Subcommittee considered that the use of natalizumab later in the course of disease (>EDSS 4.0) is likely to have fewer benefits than if used earlier. The Subcommittee considered that preventing relapses early, before EDSS 3.0 to 4.0, appears to have a greater effect on disease worsening than preventing relapses in more severe disease states (Scalfari et al. Brain 2010: 113; 1914-1929). The Subcommittee considered that treatment switching is likely to be more effective if an alternative product with a different mode of action is used.

4.7 The Subcommittee considered the data in the submission about the risk stratification of developing progressive multifocal leukoencephalopathy (PML), a potentially fatal adverse effect of natalizumab treatment. The Subcommittee noted that the risk of PML increases in patients who are (John Cunningham virus) JCV antibody positive, in patients who have previously received immuno-suppressants and as exposure to natalizumab increases.

4.8 The Subcommittee noted that approximately 50 to 70% of the population in New Zealand are JCV antibody positive with a 2% seroconversion rate per year. The Subcommittee noted that the supplier proposes to fund annual tests for JCV antibody status should natalizumab be funded and that this test would help to inform clinicians about the risk of treatment. The Subcommittee considered that a 1:100 risk of developing PML for patients with all risk factors present may be unacceptable for some clinicians and patients. The Subcommittee considered that two further concerns are: (i) the sensitivity and specificity of current JCV tests are not yet clearly established, and (ii) that natalizumab treatment may in itself increase the risk of JCV infection in those who are initially JCV negative. The Subcommittee considered that if patients are JCV positive, it may be more acceptable to use fingolimod if funded rather than natalizumab. The Subcommittee considered that should natalizumab be listed, the risk stratification should be part of the access criteria.

4.9 The Subcommittee noted a diagnostic uncertainty when PML is suspected as in MS the MRI features may be similar. The Subcommittee noted that PML is associated with approximately 20% mortality and 40% of cases are likely to result in significant disability.

4.10 The Subcommittee considered that in estimating the magnitude of effect on disease worsening, two studies (Polman 2006 and Hutchinson et al. J Neurol 2009; 256; 405-15) provide a useful basis, with the Polman trial providing stronger evidence in a heterogeneous population and the Hutchinson study providing weaker evidence in a highly selected subgroup more similar to the New Zealand treated population. With respect to disease worsening, Polman reported a relative risk reduction of 0.7 and Hutchinson reported 0.36. The Subcommittee considered that a midpoint of approximately 0.5 would be an appropriate estimate of the effect of natalizumab on disease progression for New Zealand patients.

## 5 MS Treatment Algorithms

### Application

5.1 The Subcommittee considered a PHARMAC generated proposal on potential treatment algorithms should either natalizumab or fingolimod be funded and should the entry criteria be amended to allow treatment for patients with established relapsing-remitting MS with an EDSS of less than 2.0.

**Discussion**

5.2 The Subcommittee considered that the wording in the proposed Special Authority criteria allowing treatment for patients with established relapsing-remitting MS with an EDSS of less than 2.0 be clarified. The Subcommittee **recommended** that this definition should include that the patient should have experienced at least one attack with evidence on MRI of brain lesions of different ages. Should these criteria be amended, the Subcommittee noted that the relapse criteria would also need to be amended.

5.3 The Subcommittee considered that if the entry criteria were amended as proposed, and fingolimod and natalizumab were funded, patients would begin treatment with either beta-interferon or glatiramer as first line agents. The Subcommittee considered that a reasonable trial should be done with these first line therapies, and switching should be permitted if there are no reduction in relapses and/or a significant deterioration of the EDSS.

5.4 The Subcommittee considered that natalizumab or fingolimod should be used as monotherapy, after patients had used an adequate course (at least 6 months treatment) of either beta-interferon or glatiramer or both, and had continued to deteriorate, noting that these first line treatments have more long term safety data and better cost effectiveness in first line.

5.5 The Subcommittee considered that it may be appropriate that following an EDSS increase of 2.0 or more whilst using first line therapy, patients would be required to switch to a second line treatment for a maximum of another 2 EDSS states. The Subcommittee noted that treatment is unlikely to benefit patients when EDSS is 6.0 or more. The Subcommittee considered that earlier stopping could also occur if it was clear a treatment wasn't effective or wasn't tolerated, however there is likely to be higher cost associated with using natalizumab or fingolimod earlier.

5.6 The Subcommittee considered that the use of natalizumab or fingolimod later in the course of disease (>EDSS 4.0) may have fewer benefits than if used earlier.

5.7 The Subcommittee considered that if both fingolimod and natalizumab were funded, the risk stratification for natalizumab is likely to determine which treatment is selected, with patients who are JCV antibody positive and who have used immunosuppressants in the past, likely to prefer fingolimod.

5.8 The Subcommittee considered that if a patient continued to deteriorate while using natalizumab or fingolimod, the patient is unlikely to benefit from switching to either beta interferon or glatiramer.

5.9 The Subcommittee considered that treatment switching between fingolimod and natalizumab may not be advisable, unless one is not tolerated, given the lack of evidence reviewed to date of this treatment sequencing. The Subcommittee noted that should a

patient be intolerant of fingolimod or natalizumab following a single dose or short course of treatment, then patients should be able to access the alternative product.

5.10 The Subcommittee noted that there may be some patients who could benefit from accessing natalizumab or fingolimod as a first line treatment, however it is likely that such cases be first assessed by MSTAC as both agents are not only potentially risky but there also may be difficulty in defining a patient group at this time who would benefit.

## 6 Riluzole

6.1 The Subcommittee reviewed the Special Authority criteria applying to riluzole (Rilutek) and considered that the proposed criteria was appropriate and that further targeting for patients with severe bulbar involvement was not necessary.

6.2 The Subcommittee considered that the number of patients likely to access treatment with riluzole is likely to be dependent on patient preference, and noted that approximately a third of patients would decline treatment despite being eligible. The Subcommittee noted that a similar proportion of patients who do use riluzole may stop due to side effects.

6.3 The Subcommittee considered the prevalence of amyotrophic lateral sclerosis to be approximately 4 to 6 per 100,000, with about 5% of patients surviving at 5 years following diagnosis. The Subcommittee considered the median survival from diagnosis to be 17.6 months.