Neurological Subcommittee of PTAC

Meeting held 20 September 2013

(minutes for web publishing)

Neurological Subcommittee minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2008*.

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 13 & 14 February 2014, the record of which will be available in May 2014.

Record of the Neurological Subcommittee of the Pharmacology and Therapeutics Committee (PTAC) meeting held at PHARMAC on 20 September 2013

1. Multiple sclerosis treatments

In attendance

1.1. Members of the Multiple Sclerosis Treatments Assessment Committee (MSTAC) and the Chair of the PTAC attended this segment of the meeting and were available to contribute to discussion leading to the Neurological Subcommittee of PTAC ("the Subcommittee")'s recommendations.

Application

1.2. The Subcommittee considered the PTAC's request for clinical advice regarding treatment algorithms should either natalizumab or fingolimod be funded. The Subcommittee also considered how entry criteria could be amended to allow treatment for patients with established relapsing-remitting multiple sclerosis (MS) with an expanded disability status scale (EDSS) of less than 2.0.

Recommendation

1.3. The Subcommittee **recommended** that its proposed treatment algorithm utilising natalizumab and fingolimod as first line agents for clinically definite RRMS for EDSS states 0-4 be funded with a high priority.

1.3.1. The committee **recommended** that this recommendation also include a recommendation that treatment with an interferon or glatiramer acetate for EDSS states 0 to 4.0 be funded with a high priority.

1.4. The Subcommittee **recommended** that first line treatment with fingolimod, and if not tolerated or contraindicated, an interferon or glatiramer acetate be funded for clinically isolated syndrome fulfilling the McDonald 2010 diagnostic criteria for MS with a medium priority.

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 the budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

1.5. The Subcommittee noted that there had been no head-to-head trials comparing the beta-interferons or glatiramer acetate with natalizumab. The Subcommittee considered the AFFIRM trial (Polman et al. N Engl J Med. 2006;354:899-910), a two year phase three trial of natalizumab 300mg given once every 4 weeks versus placebo for up to 116 weeks in 942 patients with relapsing multiple sclerosis. The

Subcommittee noted that natalizumab significantly reduced the risk of sustained progression of disability (HR 0.58, 95% CI 0.43-0.77, p<0.001) disability compared with placebo. The annualised relapse rate (ARR) for the treated group was 0.26 (95%CI 0.21-0.32) compared with 0.81 (95%CI 0.67-0.97) in the placebo group (p<0.001).

1.6. The Subcommittee considered the results from a study published by Hutchinson and colleagues (Hutchinson et al. J Neuro. 2009;256:405-15) and noted that although natalizumab was effective at reducing disease progression and relapses in patients with relapsing MS it may be more effective in those patients with highly active disease defined clinically or by MRI activity (enhancing lesions at baseline and those with $\geq$ 9 T2-weighted lesions at baseline). The Subcommittee noted that a paper reporting multiple subgroup analyses (Devonshire et al. Lancet Neurol. 2012;11:420-8) suggested that the effect of fingolimod was present in a number of subgroups without clearly indicating variations in effects according to MRI parameters, although numerically effects appeared larger for those patients with one or more Gadolinium-enhancing lesions compared with those with none (HR for disability progression 0.62 compared with 0.75, interaction p-value not reported) and for those with a T2 lesion volume of greater than 3300 mm^3 compared with less than 3300 mm^3 (HR 0.59 compared with 0.75, interaction p-value not reported).

1.7. The Subcommittee noted that patients who currently meet funding criteria for MS treatment in New Zealand would, as defined by the National Institute for Health and Care Excellence (NICE) in the UK, be considered to have very active disease.

1.8. The Subcommittee noted the risk of progressive multifocal leukoencephalopathy (PML) associated with natalizumab and noted that the risk of PML increases in patients who are John Cunningham virus (JCV) antibody positive, those who have previously been treated with immunosuppressants and as exposure to natalizumab increases. The Subcommittee considered that approximately 50% of the Australian population are JCV antibody positive with an estimated 2% seroconversion rate per year.

1.9. The Subcommittee considered that a positive response to JCV antibodies should not be an exclusion criterion for treatment with natalizumab, as different patients have different risk preferences and some patients who are JCV antibody positive may, in discussion with their neurologist including the risks and harms of PML and ongoing MS disease progression, wish to choose to have natalizumab if it was funded.

1.10. The Subcommittee considered that there was some anecdotal evidence to support the use of natalizumab as 6 weekly infusions, which may result in a theoretical decreased risk of PML, however, this would be off-label use and at the discretion of the treating neurologist. The Subcommittee noted that some patients who self-funded natalizumab treatment were receiving natalizumab infusions every 6 weeks to reduce the cost of treatment. However, the Subcommittee did not review any clinical trial evidence to support this.

1.11. The Subcommittee noted that natalizumab was a more potent agent than fingolimod. The Subcommittee considered for many or most cases of relapse-

remitting MS that natalizumab should be used instead of or before interferon beta and/or glatiramer acetate. However, the Subcommittee noted the risk of PML may be unacceptable to some patients considering natalizumab as a treatment. The Subcommittee noted that adherence will likely be better with natalizumab compared with fingolimod due to it being passively administered as an infusion every four weeks compared with an oral capsule daily.

1.12. The Subcommittee noted the FREEDOMS trial (Kappos et al. N Eng J Med 2010;362: 387-401) results, indicating fingolimod to be superior to placebo with a significant relative reduction in relapse rate of 54%. The Subcommittee noted that this result compared favourably, indirectly with the results in the pivotal trials for interferon beta 1 alpha, interferon 1 beta and glatiramer acetate (Avonex, Betaferon and Copaxone) which had significant reductions in relapse rates of 29% to 34% respectively.

1.13. The Subcommittee noted the TRANSFORMS trial (Cohen et al. N Engl J Med 2010), which was a one year multicentre, randomised, double-blind, double dummy, parallel group phase three study. 1,281 patients with relapse remitting MS were randomly assigned (1:1:1) to receive 12 months treatment with fingolimod 0.5 mg or 1.25 mg once daily, or interferon beta-1-alpha (Avonex) 30mcg once weekly. The Subcommittee considered that compared with 30 mcg weekly interferon beta-1-alpha (Avonex), fingolimod 0.5 mg daily was superior at reducing relapses. The annual relapse rate for fingolimod 0.5 mg was 0.16 compared with 0.33 ($p<0.001$) for interferon beta-1-alpha (Avonex). The Subcommittee noted that there was a non-significant reduction in EDSS progression.

1.14. The Subcommittee noted that the use of fingolimod would be associated with a number of additional health sector costs including cardiac monitoring at dose initiation (for bradycardia) and ophthalmology and dermatology reviews.

1.15. The Subcommittee considered the convenience of and lessened discomfort with oral dosing with fingolimod, compared with parenteral dosing with beta-interferons, to be beneficial. Members further considered that for many or most cases fingolimod would be appropriate as a first line treatment before or instead of interferon beta and/or glatiramer acetate.

1.16. The Subcommittee considered natural history data published by Confavreux et al (Brain 2003;126:770-82) and Leray et al (Brain 2010;133: 1900-13) and noted that along with clinical experience that assignment of secondary progressive status may happen at different disability levels. However, most patients with EDSS of 4.0 to 4.5 and above have secondary progressive MS. The Subcommittee noted that the conversion to secondary progressive MS in most cases manifests most clearly by increasing motor dysfunction in the legs with difficulty walking, and in practical terms an EDSS of 4.0 relates to a patient's inability to walk 500 metres without aid.

1.17. The Subcommittee considered that if a clear relapse increased a patient's EDSS to 4.5 or 5.0, but remained <5.5, then stopping treatment may disadvantage those who still have relapsing active disease and, therefore, for those patients a switch to another treatment until EDSS 5.5 would be reasonable. The Subcommittee considered the number of these patients would be low.

1.18. The Subcommittee considered that setting the entry criteria at EDSS 0 - 4.0 would be practical. EDSS 4.0 clearly measures a patient's ability to walk 500 meters without aid. By contrast, setting criteria at another EDSS level, for example EDSS 3.0, would most likely result in higher usage due to less objectivity (hence greater diagnostic discretion) at EDSS levels <4.0. The Subcommittee noted that this additional use could have issues of equity as well as economic impacts and that a criterion of 4.0 was administratively simple and more supportable clinically. Members considered the current criteria administratively complex.

1.19. The Subcommittee discussed main reasons why patients may switch treatments. In particular, members considered that a main reason for switching from natalizumab to interferon or glatiramer acetate was PML risk, while a main reason for switching from fingolimod was loss of efficacy. The Subcommittee considered that people who change from natalizumab due to the risk of PML may seek to return to natalizumab because of breakthrough disease during/following switching. Members estimated that around 2/3rds of patients who stop natalizumab due to risk would return to treatment.

1.20. The Subcommittee noted there was no evidence to support the use of interferon beta 1 alpha, interferon beta 1 beta and glatiramer acetate treatments as second line agents if a patient continued to relapse on natalizumab or fingolimod or there was progressive disability; however, the Subcommittee considered it would be difficult to predict which patients would respond to treatment with interferon beta 1 alpha, interferon I beta and glatiramer acetate.

1.21. Based on the current number of patients receiving funded treatment, and the numbers in Australia, the Subcommittee agreed with the MSTAC's estimates of likely numbers for treatment should the proposed treatment algorithm below be funded. Members took into account that treatment algorithms would allow more patients to access treatment earlier. Estimated patient numbers were interferon beta 1 alpha, interferon beta 1 beta and glatiramer acetate with 200 patients, fingolimod 500 and natalizumab 300. Members noted that currently in New Zealand 1000 patients were approved but only around 600 are currently accessing MS treatments.

1.22. The Subcommittee considered that the proposed treatment algorithm would result in an additional 80 to 100 patients in the first year being treated. The Subcommittee considered that there would be a significant budget impact associated with funding either natalizumab or fingolimod, and that at the proposed prices it may be difficult for PHARMAC to progress. The Subcommittee considered that both natalizumab and fingolimod were unlikely to provide sufficient added health benefits relative to added net health sector costs at the proposed prices compared with other applications that PHARMAC may be considering.

1.23. The Subcommittee considered that treatment should begin as soon as it was evident that the patient has relapse remitting MS with clinical and MRI evidence of relapses, with treatment matched to disease severity, and with the onset of clear secondary progression being the indication for stopping treatment. The Subcommittee noted that early effective treatment is most likely to prevent the onset of progressive disability, which, once established, is not affected by current treatment. MSTAC members **recommended** that clinical reports of attacks,

sufficiently detailed to allow independent assessment of their likely cause and severity, and MRI scans should be supplied to and verified by the MSTAC.

1.24. The Subcommittee proposed the following treatment algorithm and stopping criteria to reflect its recommendations and discussion:

- Clinically Definite Relapsing Remitting MS and with EDSS 0 - 4.0 at least 4 weeks after the start of the episode and evidence of MRI activity (either a contrast enhancing lesion on the baseline scan or with new T2 or enhancing lesions(s) on a scan subsequent to baseline):
  - One significant relapse in the previous year – the first line treatment should be fingolimod or natalizumab, and if those are not tolerated or contra-indicated, Avonex or Betaferon or Copaxone
  - Highly active- two or more significant relapses in one year, or one severe relapse – first line treatment should be with natalizumab and if not tolerated or accepted, fingolimod, interferon-1-alpha, intererferon-beta-1 beta or glatiramer acetate.

- Stopping Criteria
  - An increase in EDSS to 4.5 or above if due to slowly progressive worsening over 6 months or more i.e. due to secondary progressive disease. Switching not permitted
  - If an increase in EDSS to 4.5 or above is due to a clear relapse, a switch of treatment would be permitted if EDSS is <5.5. However, if there is subsequent progressive worsening of EDSS by one point or more due to secondary progression, continued treatment would not be approved.
  - Switching between any of the approved treatments is permitted provided the stopping criteria are not met. Continued relapses on treatment would be expected to lead to a switch of treatment.
    - If a relapse has resulted in increased EDSS that potentially may lead to discontinuation of treatment according to stopping criteria, a period of 6 months is allowed from the start of the relapse for recovery to occur.

1.25. The Subcommittee defined the following terms to apply to the proposed treatment algorithm: A significant relapse was defined as an attack sufficient to increase the EDSS or one Functional System Score (FSS) by at least one point. A severe relapse was defined as an attack sufficient to increase one EDSS FSS by at least three points for sensory, motor, brainstem or cerebellar Functional Systems or four points for visual or cognitive Functional Systems. A clear relapse is defined as one which is supported by enhancing activity on an MR scan performed at the time of the relapse or subsequent to it – either at least one new lesion compared with the most recent previous scan or any enhancing lesion; this aspect of treatment should be supervised by the MSTAC.

1.26. The Subcommittee considered that natalizumab was preferred to fingolimod, based on the net clinical effect. The Subcommittee considered that both agents would be preferred to the currently available treatments. The Subcommittee considered whether a patient being JCV virus positive was a contraindication to natalizumab, but considered that this was a risk versus benefit judgement for the patient to make in conjunction with their neurologist.

1.27. The Subcommittee considered that there was no evidence from randomised controlled trials to support the use of fingolimod or natalizumab in patients with clinically isolated syndrome, however, evidence may emerge in the future.

2. Correspondence / matters arising

Correspondence relating to riluzole

2.1. The Subcommittee considered correspondence from the riluzole consultation regarding the Special Authority Criteria for subsidy of riluzole.

2.2. The Subcommittee noted the requirement to have at least 60% of predicted forced vital capacity reflected the populations included in two pivotal trials previously considered (Bensimon et al. N Engl J Med. 1994;330:585-91; Lacomblez et al. Lancet 1996;347:1425-31). The Subcommittee noted that the Special Authority criteria reflect the evidence for the place in treatment, and its members did not consider a revision to the restrictions were necessary.

2.3. The Subcommittee considered that there were several different variants to amyotrophic lateral sclerosis and noted that patients with a variant of the disease who do not meet the Special Authority criteria may be eligible to apply under the Named Patient Pharmaceutical Assessment (NPPA) programme.

3. Apixaban for stroke prevention in atrial fibrillation

Application

3.1. The Subcommittee reviewed an application from Pfizer for the listing of apixaban (Eliquis) on the Pharmaceutical Schedule for stroke prevention in non-valvular atrial fibrillation (AF).

Recommendation

3.2. The Subcommittee **recommended** that apixaban be funded on the Pharmaceutical Schedule with medium priority for patients with non-valvular AF subject to the following Special Authority criteria:

> **Initial application** from any relevant practitioner. Approvals valid without further renewal unless notified for applications meeting the following criteria:
>
> Both:
>
> 1. Patient has been diagnosed with atrial fibrillation and requires anticoagulation; and
> 2. Patient has renal impairment with a creatinine clearance of <30ml/min.

3.3. The Subcommittee considered that it would be appropriate to fund apixaban on the Pharmaceutical Schedule without Special Authority restriction if it was cost-neutral to dabigatran.

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

3.4. The Subcommittee noted that this apixaban application has not yet been reviewed by the PTAC. The Subcommittee noted that there were two pivotal clinical studies for apixaban in AF, the ARISTOTLE trial, which compared apixaban with warfarin (N Engl J Med. 2011;365:981-92), and the AVERROES trial, which compared apixaban with aspirin in people 50 years or older with AF for whom treatment with warfarin had failed, or for whom warfarin was unsuitable or who were unwilling to take warfarin (N Engl J Med. 2011;364:806-17).

3.5. The Subcommittee considered that the clinical evidence for apixaban in AF was of excellent strength and good quality. The Subcommittee noted that the ARISTOTLE study reported apixaban to be more efficacious that warfarin in the primary outcome of ischaemic or haemorrhagic stroke and systemic embolism (hazard ratio (HR) with apixaban 0.79; 95% confidence interval [CI] 0.66 to 0.95, $p<0.001$ for non-inferiority; $p=0.01$ for superiority). The Subcommittee noted that there was no difference in the incidence of ischaemic stroke between patients treated with apixaban versus warfarin (HR 0.92, 95% CI 0.74-1.13, $p=0.42$) but the incidence of haemorrhagic stroke was lower with apixaban (HR 0.51, 95% CI 0.35-0.75, $p<0.001$). The Subcommittee also noted the results of the AVERROES study.

3.6. The Subcommittee noted that apixaban has multiple routes of elimination with only 27% being renally excreted and a significant proportion excreted faecally. The Subcommittee noted that this was different to dabigatran where 85% is excreted through the kidneys (Pradaxa Medsafe datasheet). The Subcommittee considered that renal impairment is a significant issue preventing access to dabigatran for many patients, where the patient population most susceptible to AF is also likely to be renally impaired. The Subcommittee noted that, from the available evidence, it appears that gastrointestinal side-effects are not an issue with apixaban.

3.7. The Subcommittee noted that if apixaban was funded, it would be prescribed instead of aspirin, warfarin or dabigatran. The Subcommittee noted that there were no head-to-head clinical trial data comparing the efficacy and safety of dabigatran with apixaban. The Subcommittee considered that it was difficult to compare these two treatments because the studies were performed in different trial populations with different trial designs. The Subcommittee considered that apixaban would likely be favoured over dabigatran, given its better pharmacokinetic profile in patients with renal impairment. The Subcommittee considered that, for this reason, some patients who were already stabilised on dabigatran could also be switched to apixaban if it was funded.

3.8. The Subcommittee considered that there was no evidence that any one of these treatments, dabigatran, apixaban, rivaroxaban or warfarin was safer than the others in the clinical situation where patients on these treatments develop a stroke and require thrombolysis. The Subcommittee noted that for many patients, anticoagulation is only performed 2-3 days later, and for larger strokes it is

commonly performed 10-14 days later. The Subcommittee considered that although warfarin has a specific reversal agent, unlike these new oral anticoagulants, warfarin is often not reversed in time to make a significant difference in the outcome for patients with haemorrhagic strokes. The Subcommittee considered that the availability of a reversal agent might be more relevant for patients who develop bleeding in other sites.

3.9. The Subcommittee considered that, other than drug acquisition costs, the funding of apixaban could result in increased cost to DHB hospitals when used instead of aspirin or warfarin, due to the increased use of treatments like prothrombin complex concentrates and Factor VIIa in life-threatening bleeding. The Subcommittee considered that it is unclear from current available clinical evidence how apixaban would compare with dabigatran and rivaroxaban in this respect.

3.10. The Subcommittee noted that a large proportion of patients with AF with risk factors for stroke are currently not on anticoagulation i.e not warfarin nor dabigatran. The Subcommittee considered that those most likely to benefit from apixaban are patients who cannot tolerate warfarin or dabigatran for various reasons, including if they have renal impairment which prevents the use of dabigatran. The Subcommittee considered that the AVERROES study showed that apixaban resulted in significant clinical benefit for this patient group, where the only funded alternative was aspirin. The Subcommittee considered that even if apixaban was restricted to those patients who have renal impairment, up to 50% of patients currently on dabigatran would qualify and likely switch to apixaban. As seen with the listing of dabigatran, the Subcommittee considered that the funding of apixaban would result in an increase in anticoagulant use overall.

3.11. The Subcommittee noted that the incidence of stroke was higher in Māori, Pacific peoples and people from South Asia, but considered that any benefit in stroke prevention from anticoagulation with apixaban would likely be similar be across all ethnic groups.

4. Rivaroxaban for stroke prevention in atrial fibrillation

4.1. The Subcommittee reviewed an application from Bayer for the listing of rivaroxaban (Xarelto) on the Pharmaceutical Schedule for stroke prevention in non-valvular atrial fibrillation (AF).

Recommendation

4.2. The Subcommittee **recommended** that rivaroxaban be funded on the Pharmaceutical Schedule with medium priority for patients with non-valvular AF subject to the following Special Authority criteria:

Initial application from any relevant practitioner. Approvals valid without further renewal unless notified for applications meeting the following criteria:

Both:

3. Patient has been diagnosed with atrial fibrillation and requires anticoagulation; and

4. Patient has renal impairment with a creatinine clearance of <30ml/min.

4.3. The Subcommittee considered that it would be appropriate to fund rivaroxaban on the Pharmaceutical Schedule without Special Authority restriction if it was cost-neutral to dabigatran.

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

4.4. The Subcommittee noted the results of the pivotal trial for rivaroxaban versus warfarin in AF, the ROCKET-AF trial (Patel et al. N Engl J Med. 2011;365:883-91). The Subcommittee noted that the patients enrolled in this study were a higher risk group compared with the relevant studies for dabigatran and apixaban with a mean CHADS2 score of about 3.5 (versus 2.1 for both dabigatran and apixaban) and >50% of these patients having previous stroke. The Subcommittee noted that the International Normalised Ratio (INR) was poorly controlled for patients in the warfarin arm, with patients being within the therapeutic range (TTR) only 55% of the time, but considered that low level of INR control in the trial may well be similar in the real-life clinical setting for warfarinised patients in New Zealand.

4.5. The Subcommittee noted that for the primary end point of stroke and systemic embolism, rivaroxaban was not inferior to warfarin (2.1% and 2.4% per year respectively, HR 0.99, 95% CI 0.74-1.03). The Subcommittee noted that there was no significant difference between rivaroxaban and warfarin in the primary safety end point of major and non-major clinically relevant bleeding (14.9% versus 14.5% per year respectively (HR 1.03, 95%CI 0.96-1.11, p=0.44)). The Subcommittee noted that there was significant reductions in intracranial haemorrhage (0.5% vs. 0.7%, p=0.02, HR 0.67, 95% CI 0.47-0.93) and fatal bleeding (0.2% vs. 0.5%, p=0.003) in the rivaroxaban group. However, major bleeding from a gastrointestinal site was more common in the rivaroxaban group, with 224 bleeding events (3.2%), as compared with 154 events in the warfarin group (2.2%, p<0.001).

4.6. The Subcommittee considered that one of rivaroxaban's potential advantages over dabigatran was that it was taken once per day rather than twice. The Subcommittee noted however that the half-life of rivaroxaban was similar, if not marginally less than for dabigatran and apixaban (Table 4. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. European Heart J. 2012;33:2719–2747, which highlights the potential increased risk of thrombosis to patients if a dose is missed). The Subcommittee considered that this was a significant risk given rivaroxaban would probably be preferred to other agents like dabigatran for compliance reasons but this would also be the patient group most likely to miss a dose. Although unproven, the Subcommittee considered that missing a dose of dabigatran or apixaban would likely result in less risk to a patient when compared with missing a dose of rivaroxaban. The Subcommittee also noted that cessation of rivaroxaban in the ROCKET-AF study was reported to result in more stroke or systemic embolism than in those who had been on warfarin.

4.7. The Subcommittee considered that, like apixaban, rivaroxaban would be preferred to dabigatran in patients with renal impairment, given 33% of rivaroxaban is eliminated through the kidneys compared with 85% renal elimination with dabigatran. The Subcommittee noted that rivaroxaban could be blister-packed, unlike dabigatran.

4.8. The Subcommittee considered that, other than drug acquisition costs, the funding of rivaroxaban could result in increased cost to DHB hospitals when used instead of aspirin or warfarin, due to the increased use of treatments like prothrombin complex concentrates and Factor VIIa in life-threatening bleeding. The Subcommittee noted that rivaroxaban appears more easily reversible than dabigatran, although it considered there is not good evidence to support this. The Subcommittee noted that, unlike dabigatran, rivaroxaban could not be dialysed in the event of over-dosage.

4.9. The Subcommittee noted that a large proportion of patients with AF with risk factors for stroke are currently not receiving anticoagulation treatment. The Subcommittee considered that those most likely to benefit from rivaroxaban are patients who cannot tolerate warfarin or dabigatran for various reasons, including if they have renal impairment that prevents the use of dabigatran. The Subcommittee considered that even if rivaroxaban was restricted to those patients who have renal impairment, up to 50% of patients currently on dabigatran would qualify and likely switch to rivaroxaban. As seen with the listing of dabigatran, the Subcommittee considered that the funding of rivaroxaban would result in an increase in anticoagulant use overall.

4.10. The Subcommittee noted that the incidence of stroke was higher in Māori, Pacific peoples and people from South Asia, but considered that any benefit in stroke prevention from anticoagulation with rivaroxaban would likely be similar be across all ethnic groups.

5. Everolimus for sub-ependymal giant cell astrocytomas not amenable to neurosurgical resection

5.1. The Subcommittee considered an application from a clinician on behalf of all paediatric neurologists of New Zealand for the funding of everolimus (Afinitor) for progressively enlarging sub-ependymal giant cell astrocytomas (SEGAs) not amenable to neurosurgical resection.

Recommendation

5.2. The Subcommittee **recommended** that everolimus should be listed on Pharmaceutical Schedule subject to Special Authority criteria for tuberous sclerosis patients with progressively enlarging sub-ependymal giant cell astrocytomas (SEGAs) requiring treatment. Members gave this recommendation a High Priority.

5.3. The Subcommittee further **recommended** that applications for Special Authority be limited to Paediatric Neurologists and that continuation of treatment be subject to evidence of SEGA reduction or stabilisation by 3 monthly MRI scans.

5.4. 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; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, (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

5.5. The Subcommittee noted that the application had been reviewed by the PTAC at its February 2013 and by the Cancer Treatments Subcommittee of PTAC (CaTSoP) at its September 2013 meeting. The Subcommittee noted that the PTAC had recommended that everolimus be funded with high priority for short term (6 months) treatment prior to neurosurgery in patients with SEGAs and recommended that everolimus be funded with low priority for patients with SEGAs not amenable to neurosurgical resection. Members further noted that the CaTSoP deferred making a recommendation pending further advice.

5.6. The Subcommittee noted that the tuberous sclerosis (TSC) is characterised by the failure in the regulation of mTOR and that everolimus targets mTOR. Members noted that SEGAs occur in approximately 8-20% of patients TSC and are characterised by intraventricular lesions and nodules some of which are slow growing others quiescent. Members noted that approximately 50% of SEGAs block cerebrospinal fluid (CSF) drainage which can lead to hydrocephalus, headaches, vomiting, visual disturbances, seizures, developmental delay and death. Members noted that the median age of diagnosis for SEGAs was around 8 years old but that during the natural course of disease most have stopped growing when patients reach 20 years old.

5.7. The Subcommittee noted that there is currently no effective treatment for symptomatic SEGAs. Members noted that whilst some patients currently undergo neurosurgery to remove the lesions they are rarely completely excised, therefore most patients will need repeat surgeries and the surgery itself is associated with significant morbidity and ongoing care costs. Members considered that because of the location of the lesions in the ventricles the surgery was very complex and had a high rate of immediate and ongoing complications, such as hydrocephalus, with appreciable costs.

5.8. The Subcommittee considered that there were currently approximately 400 patients in NZ with tuberous sclerosis (TSC), of whom 100 would have SEGAs with half in turn who may benefit from everolimus treatment.

5.9. The Subcommittee reviewed evidence from several studies including the EXIST 1 study (Franz et al. Lancet. 2013;381 (9861):125-32), which was a double-blind, placebo-controlled, phase 3 trial, and Krueger et al. (N Engl J Med.

2010;363(19):1801-11), which was an open label, phase 1/2 study. Members considered that overall these studies indicated that everolimus had a clinically relevant effect on SEGA reduction with around 30-35% of patients achieving a 50% volume reduction from baseline. Members noted that this effect seemed to be sustained whilst on everolimus treatment.

5.10. The Subcommittee noted that everolimus was an expensive treatment but considered that treatment would enable patients to avoid surgery, and its associated complications and morbidities, resulting in considerable cost offsets. Members considered that given the natural history of SEGAs it may be reasonable for patients to stop everolimus treatment when they reached 20 years of age so long as they continued to be monitored frequently by MRI for tumour re-growth.

5.11. The Subcommittee considered that the treatment effect for everolimus was likely a class effect, therefore, theoretically, sirolimus and temsirolimus may have similar effects at much lower costs. However, members noted that whilst there was some limited evidence of efficacy for sirolimus there was no evidence for temsirolimus Members considered there was insufficient evidence at this time to recommend use of either of these treatments in patients with SEGAs.

5.12. The Subcommittee considered that everolimus should be funded for all patients with SEGAs requiring treatment and considered it would replace SEGA neurosurgery, as most clinicians would consider the complications, morbidity and ongoing costs associated with neurosurgery to be clinically unjustifiable if everolimus were funded.

6. Gabapentin for chronic daily headache literature review

Application

6.1. The Neurological Subcommittee of the PTAC in its meeting held at PHARMAC on the 24 July 2012 had recommended that a paper be prepared reviewing the use of gabapentin for chronic daily headache.

Recommendation

6.2. The Subcommittee recommended **not** widening the present special authority restrictions for gabapentin.

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

6.3. Members noted that the Neurological Subcommittee of the PTAC in its meeting held at PHARMAC on 24 July 2012 had recommended that a paper be prepared reviewing the use of gabapentin for chronic daily headache (CHD).

6.4. The Subcommittee noted that gabapentin is currently funded on the Pharmaceutical Schedule for epilepsy and neuropathic pain with the following restrictions:

> Epilepsy
>
> Seizures are not adequately controlled with optimal treatment with other antiepilepsy agents; or Seizures are controlled adequately but the patient has experienced unacceptable side effects from optimal treatment with other antiepilepsy agents.
>
> Neuropathic pain criteria
>
> Where the patient has tried and failed, or has been unable to tolerate, treatment with a tricyclic antidepressant.

6.5. The Subcommittee noted that gabapentin is not registered in New Zealand or Australia for the treatment of CHD.

6.6. The Subcommittee noted that CDH is a descriptive syndrome encompassing a diverse group of headache disorders including some forms of migraine. Members noted that CDH classification is based on criteria developed by Silberstein and Lipton (Doddick D, Engl J Med 2006; 354:158-165).

6.7. The Subcommittee noted that headaches occurring more often than not (greater than 15 days per month) are considered to be CDHs. The Subcommittee noted that CDH can be subdivided into four categories: transformed migraine, chronic tension-type headache; new daily persistent headache; and hemicrania continua.

6.8. The Subcommittee noted that a common cause of CDH is a “transformed migraine”, which are migraines that over time become more and more frequent, blurring together until there is a 24-hour-a-day continuous background headache with occasional superimposed more severe migraine symptoms. The Subcommittee also noted that medication overuse headache (rebound) is a common cause of CDH caused by the patient’s own use of pain relievers. Members noted that an estimated 80% of patients with CDH are due to medication overuse (Doddick D, N Engl J Med. 2006;354:158-165).

6.9. The Subcommittee noted the studies provided by PHARMAC staff.

6.10. Members noted that there was only one RCT for gabapentin in CDH. Spira et al (Neurology. 2003;61(12):1753-9) compared the efficacy and safety of gabapentin (GPT) versus placebo for prophylaxis of chronic daily headache (CDH) (headache at least 15 days/month of greater than 4 hours duration over preceding 6 months). The Subcommittee noted that this was a multicentre randomised placebo-controlled crossover study. After 4-week baseline, subjects, aged 18 to 65, were randomised to GPT 2,400mg/day or placebo. There was 2 weeks titration, 6-week stable dosage, and 1 week washout period between treatment arms. The primary efficacy measure was the difference between the percentage of headache-free days per treatment period. Secondary efficacy measures included headache duration and severity, degree of disability, associated symptoms, concomitant medications, Visual Analogue Scale (VAS) scores, and quality of life (QOL). Ninety-five patients received sufficient treatment to allow evaluation of efficacy. Members noted that there was a 9.1% difference in headache-free rates favouring GPT over placebo ($p = 0.0005$). Benefits for GPT were also reported for headache-

free days/month (p = 0.0005), severity (p = 0.03),VAS (p = 0.0006), headache-associated symptoms of nausea (p = 0.03) and photophobia/phonophobia (p = 0.04), disability affecting normal activities (p =0.02), attacks requiring bed rest (p = 0.001), and quality of life (QOL) related to bodily function (p = 0.01), health/vitality (p = 0.0001), social function (p = 0.006), and health transition (p = 0.0002). Reduction in headache days/month was seen across the spectrum of prerandomisation headache frequencies.

6.11. The Subcommittee noted that the trials in this therapeutic area generally had deficits, including failure to account for medication overuse, the lack of untreated control groups (to negate the high placebo effects), lack of rigorous classification of headaches, and short time frames (of studies).

6.12. The Subcommittee noted that for prophylactic treatment with oral medication, the trials performed in the last decade report an improvement in 21% of the patients in the placebo arms. (Autret et al. J Headache Pain. 2012;13(3):191-8).

6.13. The Subcommittee noted a Cochrane Review of prospective, controlled trials of gabapentin/gabapentin enacarbil or pregabalin taken regularly to prevent the occurrence of migraine attacks, to improve migraine-related quality of life, or both. (Linde et Cochrane Database Syst Rev. 2013;6:CD010609). Members noted that the pooled evidence derived from trials of gabapentin suggested that it is not efficacious for the prophylaxis of episodic migraine in adults. Members noted that since adverse events were common among the gabapentin-treated patients, the review advocated that gabapentin should not be used in routine clinical practice. Members noted that the review concluded that gabapentin enacarbil is not efficacious for the prophylaxis of episodic migraine in adults and that there is no published evidence from controlled trials of pregabalin for the prophylaxis of episodic migraine in adults

6.14. Members considered that unless gabapentin pricing becomes more competitive as compared with other therapies for CDH, there was limited justification for widening current funding restrictions.

7. Triptan rate of onset of action literature review

Application

7.1. In its meeting held on 24 July 2012 the Neurological Subcommittee of the PTAC recommended that PHARMAC staff conduct a comparison of all available triptans (selective serotonin 5-HT1B/1D agonists), with particular focus on rate of onset of action.

Recommendation

7.2. The Subcommittee recommended **not** listing another triptan on the Pharmaceutical Schedule

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

7.3. The Subcommittee noted that in its meeting held on 24 July 2012 it had recommended that PHARMAC staff conduct a comparison of all available triptans (selective serotonin 5-HT1B/1D agonists), with particular focus on the rate of onset of action.

7.4. The Subcommittee noted that rizatriptan (10mg orodispersible tablet) and sumatriptan (50 mg, 100mg tablets, and a 12mg injection) are currently listed in the Pharmaceutical Schedule.

7.5. The Subcommittee noted the table provided by PHARMAC staff which provided a comprehensive overview of the pharmacokinetics (including the rate of action) of various triptans. (Drugs. 2000;60(6):1259-1287)

7.6. The Subcommittee noted that the triptans which have the most rapid onset of action includes the currently funded drugs, rizatriptan and sumatriptan.

7.7. The Subcommittee noted a study by Johnson and Rappoport (Drugs 2010;70(12):1505-1616) which concluded that the most effective triptans are similar in effectiveness to sumatriptan 100mg and include rizatriptan 10mg, eletriptan 40mg, almotriptan 12.5mg and zolmatriptan 2.5mg.

7.8. The Subcommittee noted that relatively few trials have compared the triptans head to head.

7.9. The Subcommittee noted a systematic review on the efficacy and tolerability of marketed oral triptans in the acute treatment of migraine. (Pascual et al Headache. 2007;47(8):1152-68). The review reported that all marketed triptans provided significant relief and/or absence of pain at 2 hours, and relief at 1 hour when compared with placebo.

7.10. The Subcommittee noted a review by Tfelt-Hansen et al (Drugs. 2000;60(6):1259-87). The review stated that sumatriptan has a low oral bioavailability and all the newer triptans have an improved oral bioavailability and for one, rizatriptan, the rate of absorption is faster. Members noted that the review stated that the half-lives of naratriptan, eletriptan and, in particular, frovatriptan are longer than that of sumatriptan but that the pharmacokinetic improvements of the newer triptans so far seem to have only resulted in minor differences in their efficacy in migraine.

7.11. The Subcommittee noted that there are three triptans available in New Zealand: sumatriptan, rizatripan and the unfunded zolmatriptan.

7.12. The Subcommittee noted that the funded triptans are contraindicated in patients taking MAOI and also have a relative contraindication in patients taking SSRIs.

7.13. The Subcommittee considered that there may be benefits from the availability of other triptans, such as fovitriptan for the treatment of menstrual migraines.

7.14. Members noted the prevalence of triptan overuse and consider that this was a public health issue. Members considered that the addition of further triptans to this therapeutic arena may have the potential to exacerbate this problem.

7.15. The Subcommittee considered that there may be a benefit in funding a triptan which could be administered nasally, such as nasal sumatriptan.