Neurological Subcommittee of the Pharmacology and Therapeutics Advisory Committee (PTAC)

Meeting held on 4 July 2018

(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 2016.*

Note that this document is not necessarily a complete record of the Neurological Subcommittee meeting; 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 1 & 2 November 2018, the record of which will be available in due course.

Record of the Neurological Subcommittee Meeting held on 4 July 2018

1. Record of previous minutes

1.1 The Subcommittee noted the record of the previous meeting that took place on 7 November 2016.

1.2 The Subcommittee considered that the minutes of the previous meeting was a true and accurate record of the meeting that took place on 7 November 2016.

2. Correspondence and Matters arising

2.1 The Subcommittee noted correspondence from the NZ Branch President of the Australasian Sleep Association, seeking widening of access to methylphenidate for disorders of hypersomnolence other than the currently funded narcolepsy indication, and widened access to modafinil for idiopathic hypersomnolence.

2.2 The Subcommittee considered that idiopathic hypersomnolence is a difficult condition to diagnose. Members considered that there could be approximately 450 people in New Zealand with this disorder, possibly more if it is a newly described disorder.

2.3 The Subcommittee noted that legislation currently restricts the prescribing of methylphenidate to specific indications (ADHD, narcolepsy and palliative care).

3. Ocrelizumab

Application

3.1 The Subcommittee reviewed a supplier funding application for ocrelizumab for the treatment of Relapse Remitting Multiple Sclerosis (RRMS).

Recommendation

3.2 The Subcommittee **recommended** that ocrelizumab should be listed in the Pharmaceutical Schedule with a medium priority. The Subcommittee considered that there was likely to be a benefit for patients who are JCV positive, but is it difficult to define the magnitude of the benefit.

Discussion

3.3 The Subcommittee considered a review article about the use of ocrelizumab in MS (Juanatey et al. Rev Neurol 2018;66:423-33). The authors conducted a literature review using the PubMed database, manuscripts published at the ECTRIMS Congress in October 2017 and active studies in Clinical Trials. Members noted that ocrelizumab is a humanised monoclonal antibody that targets the CD20 antigen on B cells. The Subcommittee noted that as CD20 is not expressed on lymphoid stem cells and plasma cells, selective depletion of cells expressing CD20 may preserve

capacity for B cell reconstitution and pre-existing humoral immunity.

3.4 The Subcommittee considered a phase II, randomised, parallel, double-blind, placebo-controlled study investigating the use of ocrelizumab in RRMS (Kappos et al. Lancet 2011;378:1779-87). Members noted that the authors concluded that the effects of B-cell depletion with both doses of ocrelizumab studied, and the effects on MRI and relapse related outcomes warranted further assessment in large, long term trials.

3.5 The Subcommittee considered the OPERA I and II studies, two identical phase III trials randomly assigning patients to receive either ocrelizumab 600 mg every 24 weeks or interferon beta-1a 44 mcg three times weekly for 96 weeks (Hauser et al. N Engl J Med 2017;376:221-34). Members considered that the studies demonstrated clinically relevant reductions in annualised relapse rate, disability progression and gadolinium enhancing lesions on MRI. Members considered the findings relating to the change in MS Functional Composite Score (MSFC) were not as robust. The Subcommittee considered that in OPERA II there was a difference in MSFC shown between treatments that was not shown in OPERA I.

3.6 The Subcommittee noted that overall adverse event rates were similar for both treatments across both OPERA I and II trials, but ocrelizumab-treated patients had a much higher rate of infusion reactions (34.3% compared to 9.7% with interferon beta-1a and placebo infusion). Members considered that infusion related reactions with ocrelizumab were more common after the first dose, and tend to become less common with subsequent doses.

3.7 The Subcommittee noted that there has been a single case of progressive multifocal leukoencephalopathy (PML) reported in a patient one month after starting ocrelizumab. Members noted that the affected patient was John Cunningham Virus (JCV) positive and had previously received natalizumab for three years. Members noted that it has been reported that this was likely a case carried over from natalizumab treatment (Mulero et al. Ther Adv Neurol Disord 2018;11:1-6).

3.8 The Subcommittee considered the reported risks of PML with rituximab, a CD20 inhibitor (Molloy et al. Arthritis Rheum 2012;64:3043-51). The Subcommittee noted that this review examined all cases of PML within the FDA Adverse Event Reporting System database and identified 39 cases of PML, of which 14 occurred with rituximab. Members noted that in the PML cases there was a reported association with systemic lupus erythematosus, pre-treatment with anti-TNF biologics, lymphopenia and cyclophosphamide therapy. The Subcommittee considered that the risk of PML with ocrelizumab is not obviously high, but noted that as lymphopenia is a known risk of treatment with fingolimod, there might be a slight increase in risk of PML with switching from fingolimod to ocrelizumab.

3.9 The Subcommittee considered that it would be reasonable to model a reduction in the number of MRI scans required compared to natalizumab. Members considered a reduction of 0.5 MRI scans per year would be reasonable to model. Members did not consider that there were any fiscal risks associated with adding another line of therapy for patients with RRMS.

3.10 The Subcommittee considered that it would be appropriate that ocrelizumab be subject to the same eligibility criteria as other high efficacy treatments if it was listed on the Pharmaceutical Schedule. Members considered patients who start treatment with ocrelizumab or natalizumab would be less likely to switch treatment than those on other treatments which have lower efficacy. The Subcommittee considered that the average number of different treatments that patients would access before reaching stopping criteria would be three.

3.11 The Subcommittee considered that the evidence provided with the application was of good quality, although limited in the number of studies available. The Subcommittee considered that there was also good supporting data available from rituximab studies in MS. Members considered that long term data and long term safety data were lacking, but this was likely to become available in time as more experience is gained with ocrelizumab.

3.12 The Subcommittee considered that the patient number estimates by PHARMAC staff were reasonable and considered that PTAC's estimates of patients likely to switch between treatments were reasonable.

3.13 The Subcommittee considered that as ocrelizumab is delivered by infusion, it would not be easy to access treatment for those who live in rural areas or are some distance from the nearest infusion service.

3.14 The Subcommittee considered the appropriate relative risk to use in economic modelling for ocrelizumab. The Subcommittee recommended using a relative risk of relapse of 0.37 and the relative risk of progression of 0.43 compared to placebo, which were derived by indirect network comparison.

4. Cladribine

Application

4.1 The Subcommittee reviewed a supplier funding application for cladribine for the treatment of relapsing remitting multiple sclerosis (RRMS).

Recommendation

4.2 The Subcommittee **recommended** that the application for cladribine be declined.

Discussion

4.3 The Subcommittee noted that cladribine is not currently registered for the treatment of RRMS in New Zealand.

4.4 The Subcommittee considered the structure and novel mechanism of cladribine, noting that the agent is being marketed as an oral selective immune reconstitution therapy. The Subcommittee noted that T and B cells have a higher deoxycytidine kinase (DCK) to 5'-nucleotidase (5'NTase) ratio compared with other cell types, which is how cladribine purportedly induces selective lymphocyte reduction.

4.5 The Subcommittee reviewed data demonstrating that cladribine significantly reduces total lymphocyte count when dosed, followed by a gradual increase in total lymphocyte count back to near normal levels over four years. The Subcommittee noted that cladribine preferentially depletes B lymphocytes compared with only a modest depletion of T cells, and that neutrophil and platelet counts remain within normal ranges during treatment. The Subcommittee noted that natural killer cell count is reduced with cladribine treatment and does not recover back to pre-treatment levels over 24 months.

4.6 The Subcommittee considered the results of the 96-week, double-blind, placebo-controlled, phase 3 CLARITY trial (Giovannoni et al. N Engl J Med. 2010;362:416-26) and the 2-year CLARITY extension (CLARITY EXT) trial (Giovannoni et al. 2017; Mult Scler. 2017; doi: 10.1177/1352458517727603), which investigated the efficacy and safety of cladribine in patients with relapsing-remitting multiple sclerosis (MS).

4.7 The Subcommittee considered that the results of CLARITY and CLARITY EXT demonstrated that most patients who received cladribine in CLARITY followed by placebo in CLARITY EXT (cumulative dose 3.5 mg/kg), or cladribine followed by cladribine (cumulative dose 7.0 mg/kg), remained relapse free up to, and beyond the four-year study period. Members noted that a higher rate of relapse was observed in patients who received placebo in CLARITY followed by cladribine in CLARITY EXT (cumulative dose 3.5 mg/kg), suggesting that a delay in treatment can negatively affect outcome.

4.8 The Subcommittee considered that the relative risk of disease progression with cladribine relative to placebo according to data from CLARITY was 0.67 (time to 3 month sustained change in EDSS score; 10.8 months in the placebo arm and 13.6 months in the cladribine 3.5 mg/kg arm). The Subcommittee considered that the annualized relapse rate in CLARITY was 0.14 for patients who received cladribine 3.5 mg/kg compared with 0.33 for patients who received placebo.

4.9 The Subcommittee considered that the duration of benefit with cladribine based on data from the CLARITY and CLARITY EXT trials is four years or more.

4.10 The Subcommittee considered that the evidence provided by CLARITY and CLARITY EXT was of good quality and had a reasonable number of patients included. Members noted that there are 10,000 patient years of trial data in these studies.

4.11 The Subcommittee noted that the overall adjusted treatment-emergent adverse event (TEAE) incidence per 100 patient years (Adj-AE/100PY) in the CLARITY, CLARITY EXT, ORACLE-MS, and PREMIERE trials was 103.29 for patients who received cladribine monotherapy compared with 94.26 for patients who received placebo; the rate of serious TEAEs was 3.57 adj-AE/100 PY compared with 4.00 adj-AE/100 PY for patients who received cladribine and placebo, respectively.

4.12 The Subcommittee noted that cladribine is registered in New Zealand for the treatment of hairy cell leukaemia (HCL), and that the dosage differs from the recommended dosage for MS.

4.13 The Subcommittee noted that oral bioavailability of cladribine is low (34% to 48%) and considered that this may cause some variability in dosing which could contribute to risk of treatment failure or reduced efficacy or adverse effects. Members noted that the half-life of cladribine is short (5.4 hours), but that the bio-pharmaceutical effects are long lasting.

4.14 The Subcommittee considered malignancy data from a meta-analysis of phase 3 trials of licensed disease modifying treatments (DMTs) for relapsing MS (Pakpoor et al. Neurol Neuroimmunol Neuroinflamm. 2015;2:e158). The Subcommittee noted that the rate of malignancy in CLARITY was 0.34% in patients who received cladribine compared with 0.0% in patients who received placebo. The Subcommittee considered that the rate of malignancy with cladribine was at the lower end of the spectrum compared to the rate of malignancy seen with the other DMTs.

4.15 The Subcommittee considered that cladribine has a different mechanism of action from other DMTs for MS. The Subcommittee noted that cladribine is a selective immune reconstitution therapy that causes a selective and transient reduction in lymphocyte number. The Subcommittee considered that this mechanism of action is different to that of fingolimod, but also has the effect of decreasing blood lymphocyte count.

4.16 The Subcommittee considered that based on the available evidence, cladribine would be an appropriate option for the treatment of RRMS. Members considered that if cladribine were to be listed, it should be subject to the same Special Authority criteria as dimethyl fumarate and teriflunomide.

4.17 The Subcommittee considered the CLARITY trial showed that after two years of treatment, 47% of participants showed no evidence of disease activity (NEDA). Members considered this was lower than the NEDA rate for fingolimod, so dimethyl fumarate and teriflunomide might be better comparators. The Subcommittee considered that pre-treatment with Cladribine might increase the risk of PML on subsequent treatment with natalizumab.

4.18 The Subcommittee considered that the weight-based dosing regimen used for cladribine is unusual with MS treatments, and that this would result in higher treatment costs for heavier patients. The Subcommittee considered that there would be reduced administration and monitoring burden with cladribine. Members considered it is likely that additional monitoring would be required in years 3 and 4 once cladribine administration had concluded.

4.19 The Subcommittee considered that if cladribine was listed, approximately 25% of patients receiving fingolimod and dimethyl fumarate may switch due to the convenience associated with administration; however, the majority of patients who would receive cladribine would be treatment-naïve.

4.20 The Subcommittee noted that there are no head-to-head trials comparing cladribine to a relevant comparator. Members considered that indirect analysis demonstrates some similarity in effectiveness with dimethyl fumarate and fingolimod.

4.21 The Subcommittee considered that there is a lack of evidence regarding treatment sequencing following cladribine treatment. Members considered that it is unclear how patients who exhibit no progression at four years should be treated subsequently, or how patients who relapsed during the treatment period should then be treated. Members noted that a persistent reduction in lymphocyte levels following cladribine treatment would likely influence and potentially limit subsequent treatment choice.

5. MSNZ

Application

5.1 The Subcommittee reviewed a funding application for widening access to multiple sclerosis treatments in four settings:

5.1.1 Clinically isolated syndrome (CIS)

5.1.2 Amending stopping criteria to EDSS 6.5

5.1.3 Amending the definition for 'significant relapse'

5.1.4 Using an alternative measurement scale to better assess fatigue and cognition.

Recommendation

5.2 The Subcommittee **recommended** that consideration could be given to targeting a subgroup of McDonald positive CIS patients with a worse prognosis to have early treatment. The Subcommittee considered that the following criteria could be used: OCB positive, OR more than 10 lesions at baseline OR a further new lesion within the first six months of diagnosis with McDonald positive MS.

5.3 The Subcommittee **recommended** amending the stopping criteria to stopping treatment on reaching EDSS 6.0.

5.4 The Subcommittee **recommended** that the application to amend the definition of a significant relapse from "at least one week" to "24 hours" be declined.

5.5 The Subcommittee **recommended** that the application to use alternative measurement scales be declined.

Discussion

Clinically Isolated Syndrome (CIS)

5.6 The Subcommittee noted that the McDonald criteria are intended to guide diagnosis of clinically definite MS (CDMS) before a second relapse has occurred. The McDonald criteria have undergone several revisions since the original version in 2001 (2005, 2010 and 2017). The Subcommittee noted that the McDonald criteria

are devised using expert consensus and empirical data, looking at which combination of MRI or laboratory findings will give the best specificity and sensitivity for subsequent development of CDMS.

5.7 The Subcommittee noted that the 2017 revision of the McDonald criteria allow that a positive oligoclonal band (OCB) test result may substitute for MRI dissemination in time (DIT). Members noted that the McDonald 2017 criteria allow treatment when the following criteria are met: One clinical attack plus two or more lesions with objective clinical evidence, DIT demonstrated by MRI or positive OCB or a further clinical episode; or One clinical attack with objective clinical evidence of only one lesion, dissemination in space (DIS) demonstrated by a further clinical attack in a different site or by MRI and DIT demonstrated by MRI or positive OCB or a further clinical episode.

5.8 The Subcommittee considered that if funded access was widened to include McDonald CIS, the time on treatment would be increased for patients identified with McDonald CIS as they would start treatment before a second clinical episode. The Subcommittee considered that there could be approximately 65 patients per year for two years receiving earlier treatment. The Subcommittee considered that as the McDonald criteria do not have 100% specificity, approximately 15% of the patients with McDonald CIS would not go on to develop CDMS and would therefore be treated unnecessarily.

Stopping criteria

5.9 The Subcommittee considered that if access to MS treatments was widened to EDSS 0-6.0 inclusive, there would likely be an additional 800 patients eligible for treatment. The Subcommittee noted that clinical trials with the newer agents have recruited patients with EDSS range 0-5.0 or 0-5.5. Members considered that groups above and below EDSS 3.5 have been shown to benefit from disease modifying treatments (DMT). The Subcommittee considered that there is evidence that a reduction in lesion load may lead to better cognitive outcomes and preserved upper limb function, which the EDSS scale is not sensitive to at scores greater than 4.5. The Subcommittee considered that relapse rate and MRI activity is lower in more advanced MS, so DMTs are less effective at higher EDSS scores.

5.10 The Subcommittee considered that it would be reasonable to remove the gradient scale ie. remove stopping criteria below EDSS 4.5, which would level the playing field for all patients and reduce the administrative burden for neurologists.

Definition of Significant Relapse

5.11 The Subcommittee noted that the median time to achieve 50% of eventual recovery in optic neuritis was approximately 15 days. The Subcommittee considered that a 24-hour duration for a significant relapse was too short and not very practical. The Subcommittee **recommended** that the application to amend the definition of a significant relapse from “at least one week” to “24 hours” be declined.

Alternative measurement scales

5.12 The Subcommittee considered that measurement scales other than EDSS were impractical and likely lead to patients stopping treatment earlier, as they are potentially more sensitive to disease progression at higher EDSS states. The Subcommittee **recommended** that the application to use alternative measurement scales be declined.