Pharmaceutical Technical Advisory Committee
PHARMAC
PO Box 10-254
Wellington 6143

8 September 2017

Dear PTAC,

RE: Request for consideration of funding Ocrelizumab for Primary Progressive MS from The Multiple Sclerosis Society of New Zealand (Inc)

The Multiple Sclerosis Society of New Zealand is aware that Roche NZ is making a submission to request Ocrelizumab be listed on the Pharmaceutical Schedule for the treatment of Primary Remitting MS (PPMS). We are writing in support of this application.

Note: We have made a separate submission for the inclusion of Ocrelizumab for Relapsing Remitting MS (RRMS).

Primary Progressive MS in NZ

It is well known that many people with PPMS will not have seen a Neurologist in many years and there is currently no MS registry, therefore, the exact number of PPMS patients in NZ is unknown. However, based on the 2006 NZ MS Prevalence Study which recorded 457 people with PPMS,[1] [2] compared with the 2012-14 Incidence Study, population growth and morbidity estimates and the understanding that PPMS constitutes 10-15% of the MS population there are thought to be 400-600 people in New Zealand living with PPMS.

On average people are diagnosed with PPMS at a later age than RRMS, with onset at an average of 40 years, rather than 30, and unlike RRMS there is no significant disproportion between men and women (1:1).[3] There is also no obvious latitudinal influence as noted with PPMS.

The Impact of Primary Progressive MS

Unlike the more common RRMS which is characterised by episodic relapses, periods of remission and often long periods of no symptom presentation, PPMS is distinguished by a steady progression of the condition, with worsening disability over time. Symptoms experienced with PPMS do not return to the pre-worsened state, or near, as they do following a RRMS episode.

For those with PPMS the initial presentation found in 80% of patients is a progressive spastic paraparesis, usually in the legs.[4] Often people with PPMS will lose the mobility of their legs first, with symptoms then moving up the body. Therefore, people with PPMS will likely loose leg function first but still maintain full arm function, until that may eventually worsen over time. Mobility issues are

[1] Taylor, B. V. MS Prevalence in New Zealand; an ethically and latitudinally diverse country. Mult Scler. 2010 Decl 16 (12): 1422-31
[2] The Incidence of Demylinating Disorders in New Zealand. Final report for the MS Incidence Study prepared by Dr Deborah Mason for the Multiple Sclerosis Society of NZ (2017)
[3] Koch, W. M., et al. The natural history of early versus late disability accumulation in primary progressive MS. J Neurol Neurosurg Psychiatry. 2015; 86: 615-621.
[4] Millar, D. H., Leary, S. M. Primary Progressive Multiple Sclerosis. The Lancet. Neurology. Oct 2007. Vol 6. 903-912

more common in those with PPMS than sensory, such as weakness, impaired mobility, stiffness, difficulties lifting and moving the leg causing a drag and fatigue. Fatigue in PPMS is correlated to disease progression[5]. In turn fatigue in PPMS impacts on physical, cognitive and psychological functioning. Other common and often distressing symptoms include pain, tingling, numbness, urgency, constipation, incontinence, and in men, erectile dysfunction. Cognition is also affected impacting attention spans, working and verbal memory, spatial reasoning and verbal fluency. Depression also affects at least 50% of the MS population.[6]

There is a high unmet medical need in those with PPMS and Ocrelizumab is the first Disease Modifying Treatment (DMT) that has shown significant clinical benefit to those with this form, slowing or halting the disabling effects of the condition, the goal for PPMS treatments being researched.

Ocrelizumab for PPMS has now been made available in the USA through the FDA and is undergoing funding review in Australia. The treatment for PPMS has also been supported by the International Progressive MS Alliance:

"We are encouraged with the continued focus of the regulatory agencies and progress being made to bring forth treatments for this disabling form of MS. While the reported effects for ocrelizumab on progression are modest, the data clearly indicates that this treatment has potential benefit and is not only a source of hope, but also an important milestone that will further inform development for effective treatments for everyone with progressive forms of MS." Professor Alan Thompson, Chair of the International Progressive MS Alliance Scientific Steering Committee.[7]

Early Intervention

In the early stages of MS the damage that occurs, particularly in progressive forms, can have a marked impact on cognition, mobility, emotional well-being, quality of life and the ability to do day-to-day activities such as work or care for yourself. As MS progresses and disability increases these are even more severely impacted and with PPMS they are irreversible. MSNZ has officially endorsed the recommendations that MS organisations and key MS clinicians worldwide recommend that early diagnosis and treatment is crucial for limiting and managing the irreversible, progressive deterioration[8]. As MS is a chronic and complex condition highly effective treatments need to be made available as early as possible in the disease course.

Over time MS becomes increasingly burdensome on the individual and their families leading to substantial economic losses for society, owing to diminished working capacity. With 134 people with MS being diagnosed every year in New Zealand early intervention is vital.[9] Early access will enable people with MS in NZ to minimise the impact of the condition, reducing disability, cost to the individuals and health system in the long-term and improving their overall health and well-being.

[5] Miller, D. M. et al. The Association Between Confirmed Disability Progression and Patient-Reported Fatigues in PPMS Patients in the ORATORIO Study. NCT01194570. Presentation
[6] Holland, N. J., et al. Meeting the Needs of People with Primary Progressive Multiple Sclerosis, Their Families, and the Health-Care Community. Int J MS Care. 2011 Summer; 13(2): 65-74
[7] www.progressivemsalliance.org/announcements/fda-grants-priority-review-for-ocrelizumab-in-primary-progressive-and-relapsing-ms/
[8] Giovannoni, G. *et al*. Brain Health: Time matters in multiple sclerosis (2017) www.msbrainhealth.org
[9] The Incidence of Demylinating Disorders in New Zealand. Final report for the MS Incidence Study prepared by Dr Deborah Mason for the Multiple Sclerosis Society of NZ (2017)

Clinical Benefits

Clinical Data

The Phase III study (ORATORIO) involved 732 participants with PPMS was undertaken over a 120-week period. Results clearly showed evidence of reduced signs of disease activity in the brain (MRI lesions) compared with placebo with a median follow-up of three years. The ORATORIO study met its primary endpoints, being the first involving PPMS patients to do this. The results showed that at 120-weeks:

- on the timed 25-foot walk worsened only by 38.9% in those taking ocrelizumab versus 55.1% worsening in those on placebo
- the total volume of brain lesions on T2-weighted magnetic resonance imaging (MRI) decreased by 3.4% with ocrelizumab and increased by 7.4% with placebo
- the percentage of brain-volume loss was 0.90% with ocrelizumab versus 1.09% with placebo

No Evidence of Disease Progression (NEP)

The primary goal for any PPMS treatment is NEP. In the ORATORIO study NEP was assessed by the combined absence of 12-week clinical progression as measured by:

- No confirmed disability progression as measured by 'EDSS'
- No confirmed progression on upper limb function as measured by '9-hole Peg Test'
- No confirmed progression on ambulation as measured by 'Timed 25-Foot Walk'[10]

The results showed that:

- 43% of ocrelizumab patients had No Evidence of Progression (NEP) versus 29% for placebo patients
- Where NEP status was reached shows no worsening in three major components of MS disability, a major outcome for PPMS patients

Whilst some may consider the successes "modest", for those New Zealanders living with PPMS, the most aggressive, disabling and life altering form of the condition, these results provide hope. Many are told that there is nothing that can be done for them however Ocrelizumab will potentially slow or halt the progression of disability, reduce their fatigue and improve their mental quality of life.

Fatigue Reduction

For people with MS fatigue is one of the most common and debilitating symptoms with estimates ranging between 75-90% of those diagnosed impacted. PPMS patients have a significantly high level of fatigue impacting their quality of life. In the ORATORIO trial at the baseline 62.7% of participants reported significant levels of fatigue on the Modified Fatigue Impact Scale (MFIS)[11]. There are currently no treatments available to reduce fatigue for PPMS patients.

[10] Montalban, X. et al. Evaluation of No Evidence of Progression Using Composite Disability Outcome Measures in Patients With Primary Progressive Multiple Sclerosis In ORATORIO Trial. Presented at ECTRIMS 2016: Platform Number 167.
[11] Miller, D. M. et al. The Association Between Confirmed Disability Progression and Patient-Reported Fatigues in PPMS Patients in the ORATORIO Study. NCT01194570. Presentation

Patient-Reported Outcomes (PROs)

The PROs[12] of the ORATORIO study provide valuable insights into the benefits from the patients' perspectives. The value of PROs for PPMS patients is important as health-related reduction in quality of life is relatively high. Important outcomes were compared to those on placebo that Ocrelizumab significantly:

- improved mental health measures for quality of life
- reduced fatigue from the patients' perspective.

There is currently one person with PPMS on Ocrelizumab in NZ who is a part of the trial. His sentiments echo what many with PPMS would like to achieve from a treatment, a maintenance rather than further progression of disability; "to date my abilities have remained much the same as they were when I commenced the trial. Walking distances, walking speed, memory, neurological tests, and all other tests have been very consistent. I am very happy with my results."[13]

Proposed Criteria

We have been involved in the discussions around the proposed criteria for Ocrelizumab for PPMS. We understand that with the aims of the treatment being to halt or slow clinical progression, including in ambulation and upper body function this is being presented as:

- Clinical diagnosis of PPMS under the 2010 MacDonald Criteria
- Entry EDSS 2-6.5
- Stopping EDSS 7 with no ladder
- No history of relapsing MS

We understand this is based on the trial criteria however we would support use up to 8.5 enabling those still with upper body, arm, use to receive benefit from the treatment. Many people with a disability, including MS, can still have a good quality of life with arm function.

We see it as extremely important not to impose the ladder system imposed on the RRMS DMTs on this treatment as the likelihood of progression is higher with PPMS and a slowing as much as halting is equally as important positive outcome.

Side Effects

As with the RRMS trials, the ORATORIO trial showed no evidence of the potentially life threatening PML Virus. There was a slight increase in reported cases of oral herpes, infusion related reactions, upper respiratory tract infections and 2.8% compared to the placebo's 0.8% occurrence of neoplasms. Due this these slight increased risks regular monitoring and increased education among prescribers should be supported. Neurologists will need to ensure that they are providing their patients with comprehensive information regarding the risks and benefits of these treatments to allow them to make informed choices. Pre-treatment tests and reviews of a patient's history for predispositions, where possible, for cancer, particularly breast cancer, and oral herpes should be required for people considering using Ocrelizumab, just as the JCV virus is tested for Tysabri. While

[12] De Seze, J. et al. Patient-Reported Outcomes in the Phase III Double-Blind, Placebo-controlled ORATORIO Study of Ocrelizumab in Primary Progressive Multiple Sclerosis. Poster Presented at ECTRIMS 2016: 14-17 September.
[13] Multiple News: Multiple Sclerosis Auckland Magazine. Issue 37: June 17. P19

these medical conditions are not uncommon for Health Professionals to see, it will be important to ensure they are aware that they are potential side effects their patients may present with and to catch them in their early stages. GPs can play an integrated role in supporting people with MS to make informed decisions and provide care beyond the neurologist.

Potential role of MS Organisations

We expect, based on initial feedback since the FDA approved use in March 2017, a significant amount of interest from people with PPMS in this treatment. There will certainly need to be education around the treatment, the criteria and who will be able to access this. MSNZ would like to offer its support in ensuring that the information is circulated. MS Field Workers across the country may also be in a position to triage questions they may receive from clients, assisting the already under-resourced Neurology departments across the country by responding to some of the queries and supporting their clients with the decision outcomes, whether they qualify for treatment or not.

Future Considerations

MSNZ strongly believes that people with MS, whether on treatment or not, should be able to access an annual review. Regular monitoring of the disease and recording of information formally are a key part of any successful disease management strategy. Regular monitoring will generate long-term real-world evidence that organisations such as PHARMAC and clinicians can use for evaluating therapeutic strategies.

With no current MS Registry, understanding the potential uptake and impact of new treatments is restricted. A nationwide MS Registry would be highly beneficial for PHARMAC, DHBs clinicians, MS organisations.

Closing Remarks

We thank you for considering Ocrelizumab to be listed on the Pharmaceutical Schedule for both PPMS and RRMS. We have received a significant amount of positive interest from the MS Community in seeing Ocrelizumab becoming available for funding and we hope the application will be looked upon favourably for the benefit of people with Multiple Sclerosis in New Zealand. Supporting the access to appropriate lifestyle interventions and treatment such as Ocrelizumab has the potential to have a positive impact on the individual in a health and quality of life perspective as well as to the long-term costs of MS to the NZ economy. We urge PHARMAC to not delay any further in making a positive decision on this as for those with PPMS, disability progression can happen rapidly and for many there is an urgency in beginning treatment as early as possible to be given the chance to best respond positively.

Kind Regards,

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