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Multiple Sclerosis New Zealand

23 April 2019

Dear Adrienne

RE: Urgent clinical need for ocrelizumab PHARMAC funding for people with Relapsing Multiple Sclerosis (PwRMS)

The Multiple Sclerosis Society of New Zealand (MSNZ) has received feedback from NZ neurologists across the country on the potential clinical impact of the continued delay to PHARMAC funding of ocrelizumab for RMS.

On behalf of the NZ MS community who are impacted by the slow processes, we have consolidated the clinicians' feedback and are sharing this with PHARMAC. MSNZ strongly supports their valid concerns which we urge you to consider and ask that you fast track the process.

We would also like to highlight a number of other key considerations which support the need for funded ocrelizumab as a treatment option for NZ PwRMS.

We note from the PHARMAC tracker that the PTAC review of ocrelizumab for RMS (funding submission May 2017) is complete, with the recommendation to fund if cost neutral to other currently funded therapies. We ask that you provide an update as to the expected time this should take.

JCV-positive patients who are taking natalizumab

Natalizumab is working extremely well for many PwRMS nationwide. However, NZ neurologists have increasing concern that further delays to funding ocrelizumab will continue to increase the risk of progressive multifocal leukoencephalopathy (PML) for JCV-positive patients who are taking natalizumab. The majority of neurologists we have spoken to have patients who they would switch immediately to ocrelizumab.

As stated above, under the current PHARMAC funding criteria, patients eligible for treatment would meet the definition of moderate disease activity as a minimum and be considered for a high-efficacy treatment (Pardo & Jones 2017).

In NZ, natalizumab is currently the only PHARMAC funded high efficacy disease modifying therapy for RMS. NZ neurologists and JCV-positive patients who are taking natalizumab currently face a very difficult decision to either switch to a potentially lower efficacy disease modifying therapy, which may lead to increased disability, or continue natalizumab treatment with the higher risk of PML.

NZ neurologists have commented 'it keeps us awake at night'; 'we're concerned about the legacy we are leaving'.

We are also aware of some patients who have declined their neurologist's recommendation for natalizumab treatment due to their concerns regarding PML risk.

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JCV sero-prevalence in MS cohorts is around 55%. In addition, JCV sero-conversion in natalizumab-treated patients is three to four times higher than age-based conversion rates. A mean of 10.8% sero-negative patients changing to sero-positive per year on treatment has been reported (Scwab et al 2018).

The rate of PML in JCV-positive patients increases with length of treatment. For patients with > 2 years duration of therapy and prior exposure to immunosuppressants, it has been estimated to be as high in 1/44 (Berger & Fox 2016).

Funding for natalizumab has now been available in New Zealand for over 4 years (from 1 Nov 2014). Data from July 2018 (PHARMAC OIA) note there are 367 NZ patients receiving natalizumab. Although we are not aware of any national data on the proportion of these patients who are JCV positive, the first NZ case of natalizumab associated PML occurred at Waikato DHB in 2018.

Feedback from the neurologists is that data supports ocrelizumab as a high efficacy option (data summarised below) and offers a solution to this important concern. This is in alignment with the recent neurological sub-committee feedback.

All NZ PwRMS should have access to ocrelizumab

As noted in our letter from 22 May 2017 it is important that a full range of therapies are available to allow neurologists and PwMS the scope and flexibility to be able to find the best option for the individual. This is in keeping with international best practices as agreed by leading international neurologists and over 40 MS national MS organisations worldwide who endorse MS Brain Health.

We believe people with active MS should be given the most effective treatment options available to prevent relapse and subsequent disability. High relapse activity, in particular whilst on treatment, is linked to an increase in disability (Jokubaitis et al 2016). However, failure on one treatment does not mean the patient will not benefit from another treatment. Therefore, it is also important to have a comprehensive range of options available to enable PwMS and their clinician to find the best treatment solution for the individual.

Data supports ocrelizumab as high efficacy treatment for NZ PwRMS (see below).

Potential uses and characteristics of ocrelizumab for PwRMS include:

- A high efficacy option for PwRMS at diagnosis or for those with ongoing disease activity on oral treatments.
- A high efficacy option for JCV positive patients at risk of PML.
- A high efficacy option for those with contraindications to or side effects and/or tolerability issues on oral treatments.
- Reduced administrative burden - 6 monthly infusions versus natalizumab 4 to 6 weekly. This reduction in frequency of administration would significantly reduce the burden of receiving treatment for PwMS in particular for those:
    - Living some distance from infusion centres
    - Needing to take time off from work or young parents needing to make child care arrangements for infusions
- No potential compliance issues or daily reminders that they are living with MS compared with oral treatments.
- Minimal ongoing monitoring reducing demands on stretched NZ neurology resources.

Ocrelizumab efficacy & safety

In our previous letter regarding ocrelizumab for RMS (22 May 2017) we shared data from the OPERA studies which compared ocrelizumab 600 mg with an active comparator, interferon β-1a 44 µg.

Many clinical trials have assessed the efficacy and safety of MS treatments but a comparative randomised trial of all DMTs has not been conducted and is unlikely to occur in the future. In the absence of such a trial, network meta-analyses (NMAs) can be helpful to indirectly compare treatments.

From the recent literature search there are 5 NMA published that include ocrelizumab in their analysis. In addition to NMAs, two of these report 'surface under the cumulative ranking analysis' (SUCRA) values, which increase the precision of estimation of the relative effect sizes of comparisons (Lucchetta et al 2018; McCool et al 2019).

Lucchetta et al conclude:

- High-quality evidence shows that alemtuzumab, natalizumab and ocrelizumab present the highest efficacy among DMTs.
- RRMS guidelines should consider a three-category classification: high efficacy (i.e. alemtuzumab, natalizumab, ocrelizumab), intermediate efficacy (i.e. cladribine, fingolimod, dimethyl fumarate) and low efficacy (i.e., glatiramer acetate, beta-interferons and teriflunomide).

We would also like to make you aware that the Multiple Sclerosis International Federation has made a submission to the World Health Organisation to have Ocrelizumab listed as one of three MS treatments on the Essentials Medicines List.

McCool et al concluded that 'results suggest that ocrelizumab has an efficacy superior to or comparable with all other currently approved DMT's across all endpoints analysed'. Specifically, for ocrelizumab and natalizumab the SUCRA rankings were (Range 0-100%; higher values better treatment):

- Annualised relapse rate - ocrelizumab 88.9%; natalizumab 92.7%
- 12 week confirmed disability progression - ocrelizumab 95.5%; natalizumab 71.2%
- Serious adverse events - ocrelizumab 78.7%; natalizumab 64.2%
- Discontinuation due to adverse events - ocrelizumab 60.0%; natalizumab 63.9%

Over 80,000 patients have now been treated with ocrelizumab globally (https://www.ocrelizumabinfo.global/).

As of December 2018 there have been 6 confirmed cases of carry-over PML in MS patients treated with ocrelizumab, 5 of these have been assessed as related to natalizumab and 1 to fingolimod. No unconfounded PML cases have been reported in patients receiving ocrelizumab. https://www.ocrelizumabinfo.global/content/dam/Ocrelizumab/en/publications/111522802FactsheetPMLv2.pdf

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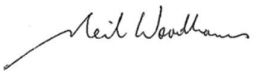
Given the important information highlighted above we ask PHARMAC to urgently fund ocrelizumab as a treatment option for all people with relapsing MS in New Zealand.

Yours faithfully



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References

Berger JR, Fox RJ. Reassessing the risk of natalizumab-associated PML. J Neurovirol. 2016;22(4):533-5.
Jokubaitis et al. Predictors of Long-Term Disability Accrual in Relapse-Onset Multiple Sclerosis. ANN Neurol 2016;80:89–100.
Lucchetta R et al. Disease-modifying therapies for relapsing-remitting multiple sclerosis: a network meta-analysis.
McCool et al. 2019. Systematic review and network meta-analysis comparing ocrelizumab with other treatments for relapsing multiple sclerosis.
Pardo & Jones. The sequence of disease-modifying therapies in relapsing multiple sclerosis: safety and immunologic considerations. J Neurol (2017) 264:2351–2374.