[redacted]

8.5. MSTAC noted that PHARMAC had received a funding application from Roche for ocrelizumab and that it was currently unregistered. Members commented that ocrelizumab has a risk of PML.

[redacted]

8. Multiple Sclerosis Society of New Zealand (MSNZ) request to widen access

Application

8.1. MSTAC considered the application for widening access to MS treatments submitted by the MSNZ in addition to the minutes relating to PTAC's review of that application.

8.2. MSTAC **recommended** allowing starting treatment and treatment switching up to EDSS 4.5, irrespective of starting EDSS. MSATC considered that stopping at EDSS lower than 4.5 was not the best clinical decision for most patients. MSTAC considered that it would be advantageous to allow treatment switching and treatment right up to EDSS 4.5 irrespective of the starting EDSS. MSTAC considered that this was the highest priority of all its recommendations.

8.3. PHARMAC staff queried the suitability of using the estimates of relative risks beyond EDSS 4.5. MSTAC noted that the applicability of relative risk of progression, and the relative risk of relapses adopted in the PHARMAC economic model would be applicable up to EDSS 5.5 as this was the usual upper EDSS limit in the clinical trials of relapsing MS. MSTAC noted that a substantial proportion of this group of patients will have secondary progressive disease, but to enter the trials they had to have relapses as well, in line with PHARMAC criteria which include patients with secondary progressive disease as long as they have relapses.

8.4. MSTAC considered that the paper by Palace et al (BMJ Open, 2014;4) (Table 3) may be better than the older London, Ontario data (Weinshencker et al) to use

for background natural history and noted that they could provide further comment at a later stage if required. MSTAC noted that the paper by Palace et al addresses the probability of untreated patients going from one EDSS state to all the other EDSS states each year.

Stopping Criteria

8.5. MSTAC noted that EDSS 5.5 is easily quantifiable by the walking distance requirement of 100m without aid or rest. MSTAC considered that there would not be a large number of patients at EDSS 5.5 as they move through these steps quite rapidly and spend longer at EDSS 6 and 6.5. Patients stay in EDSS 6 and 6.5 for approximately 4 years compared with 2 years for earlier states with impairment of walking.

8.6. MSTAC considered that there was some evidence of benefit to extend treatment up to EDSS 5.5, but less to support extending treatment up to EDSS 6.5. MSTAC considered it was unable to provide an estimate of relative risk of disease progression above EDSS 5.5 due to lack of evidence.

8.7. MSTAC **recommended** widening access by amending the stopping criteria, in the following order of priority, for all funded treatments:

1) All existing funded patients have stopping on reaching EDSS of 4.5 not dependent on starting EDSS.
2) All patients have stopping on reaching EDSS of 5.5, not dependent on starting EDSS.
3) All patients have stopping on reaching EDSS of 6.5, not dependent on starting EDSS.

8.9. MSTAC considered that if patients with a low EDSS have modest activity of their MS, this can lead to them reaching their stopping criteria quickly. MSTAC considered that a stopping criterion of 4.5 for these patients would be clinically more appropriate.

Clinically Isolated Syndrome

8.10. MSTAC considered that treating patients with Clinically Isolated Syndrome (CIS) who fulfil the McDonald 2010 diagnostic criteria for MS was supportable in some cases, but there is a risk of treating patients who do not go on to develop Clinically Definite MS (CDMS). MSTAC considered it would be clinically appropriate to treat patients with CIS, and McDonald MS if they had an attack characteristic of MS with a scan showing clear-cut MS lesions.

8.11. MSTAC considered that there is little long term follow up data on the number of patients who have McDonald MS according to recent criteria who do not go on to develop CDMS. MSTAC noted that recent data (Filippi et al. Lancet Neurol. 2018;17:133-42) showed approximately 49% of all CIS patients had not converted to CDMS after 5 years, with about 70% of patients who fulfilled 2010 McDonald criteria at baseline converting to CDMS within 5 years.

8.12. MSTAC considered that there is no conclusive evidence that early treatment of patients with McDonald MS provides additional benefit.

8.13. MSTAC considered that treating patients with CIS would increase the number of people on treatment by treating 10-15% of a CIS patient group who wouldn't fulfil the current criteria, and treating patients for a longer duration as they are starting treatment earlier in the disease course.

8.14. MSTAC considered that there is more evidence for using glatiramer acetate and the beta-interferons in CIS than for the higher efficacy products. MSTAC considered that the preferred approach if treating McDonald MS, might be to start patients on glatiramer acetate or one of the beta-interferons and switch to a higher efficacy product if they had a relapse. This approach would reduce ill-effects from higher efficacy products.

8.15. MSTAC considered that there was a group of patients who would fulfil the McDonald criteria for MS that would benefit from treatment. MSTAC considered that further guidelines/restrictions would need to be developed to treat CIS patients. These could include factors such as assessing the severity of changes on MR scans e.g. multiple gadolinium enhancing lesions and the extent of T2 lesions. MSTAC noted that the Queen Square data showed increasing risk of early conversion to CDMS based on the number of T2 lesions on brain MR scan on presentation with CIS.

8.16. MSTAC **recommended** widening access to patients who fulfil the McDonald criteria for MS, with restrictions that are yet to be developed.

Definition of Significant Relapse

8.17. MSTAC considered that the intent of the Significant Relapse period was to ensure that symptoms were not transient and were in fact due to a relapse.

8.18. MSTAC considered that if a significant relapse was defined as 24-48 hours then patients might meet their stopping criteria more quickly and be required to switch or come off treatment sooner.

8.19. MSTAC **recommended** that amending the definition for significant relapse should be declined. The Committee noted that a significant relapse is defined to be at least a week to give a clear indication that the new symptoms are due to a new active inflammatory process.

Measurement Scales

8.20. MSTAC considered that the MS Functional Composite (MSFC) score was more objective and potentially more sensitive to change than EDSS, but was limited by threshold effects. In practice it is not always as reliable as a measure of change as EDSS and it would take quite some time in clinic to perform. The panel noted that funding bodies such as the FDA have not yet accepted it.

8.21. MSTAC considered that it is difficult to include fatigue as it is very difficult for clinicians to quantify. Cognition is included in the EDSS and potentially has a significant effect on the EDSS in the lower EDSS range.

8.22. MSTAC **recommended** that using an alternative measurement scale to better assess fatigue and cognition be declined.

9. Ocrelizumab for Relapsing-Remitting Multiple Sclerosis

9.1. MSTAC considered the funding application from Roche Products (New Zealand) Limited for ocrelizumab for relapsing remitting MS, in addition to the minutes relating to PTAC's review of the application.

9.2. MSTAC considered that there was a small risk when using ocrelizumab in JCV antibody positive patients. The panel considered that it is a substantially smaller risk than with natalizumab.

9.3. MSTAC considered that most JCV antibody positive patients on natalizumab would switch to ocrelizumab.

9.4. MSTAC considered that listing ocrelizumab would be unlikely to increase the number of new people on treatment, but would potentially have a substantial effect on prolonging the duration of treatment, while also providing substantial health benefits.

9.5. MSTAC considered that patients would be likely to remain on their current treatment if stable, with the exception of JCV antibody positive patients with a high titre, who would be likely to switch from natalizumab to ocrelizumab.

9.6. MSTAC considered that if ocrelizumab was funded, it should have the same Special Authority restrictions as the currently listed high efficacy treatments.

9.7. MSTAC noted that there are a number of patients on ocrelizumab overseas who are also being given IVIG, which could lead to significant additional costs to DHBs if this practice occurred in New Zealand.

9.8. MSTAC considered it appropriate to switch between ocrelizumab, natalizumab, fingolimod, dimethyl fumarate and teriflunomide under the current criteria.

9.9. MSTAC considered ocrelizumab could have higher suitability than natalizumab as it would decrease the burden of regular infusions for caregivers and patients, especially those living some distance from the infusion service.

9.10. MSTAC noted that there is an increasing view that patients should be having 12 monthly MR scans but this is not always being done. The panel considered that JCV antibody positive patients on natalizumab who switch to ocrelizumab will require fewer MR scans and noted that this was discussed in the supplier application as potentially reducing treatment costs.

9.11. MSTAC considered it more appropriate to use a cost utility analysis than a cost minimisation analysis for this application, as the proposed listing provided health gains over the status quo, in particular due to lower rates of disease progression.

9.12. MSTAC considered the relative risk of disease progression (EDSS worsening) for a patient on ocrelizumab relative to placebo is 0.43.

9.13. MSTAC considered the relative risk of a disease relapse for a patient on ocrelizumab relative to placebo is 0.37.

9.14. MSTAC considered the likely market dynamics from a listing of ocrelizumab. The Committee noted that their estimates were broadly in line with PTAC.

9.15. MSTAC considered that almost every patient who was JCV antibody positive with a high titre would switch from natalizumab to ocrelizumab. This might be up to 15 to 20% of natalizumab patients.

9.16. MSTAC considered that approximately 80% of patients on natalizumab are JCV negative or low titre JCV antibody positive, so would not expect these patients to switch.

9.17. MSTAC considered that about 30% of JCV antibody negative patients who would otherwise have started on natalizumab would start ocrelizumab mainly because of demographic factors, such as rural patients not easily able to access infusion services regularly.

9.18. MSTAC considered that about 30% of patients on fingolimod would switch to ocrelizumab.

9.19. MSTAC considered that about 30% of patients on dimethyl fumarate would switch to ocrelizumab.

9.20. MSTAC considers that in the long term, up to 50% of patients on oral treatments would start on ocrelizumab.

9.21. MSTAC **recommended** that ocrelizumab be funded with a high priority.

10. Ocrelizumab in Primary Progressive Multiple Sclerosis (PPMS)

10.1. MSTAC considered the minutes from the February 2018 PTAC meeting, noting that PTAC had recommended that the application for ocrelizumab in PPMS be declined.

MSTAC considered that patients with PPMS who have evidence of active disease on MR scan should have access to funded ocrelizumab. The panel considered that this group has a high health need with no alternative treatments.

10.2. MSTAC noted the ORATORIO trial population composition was unusual, with 25% having MR gadolinium enhancing lesions. However, the panel considered that the statistical analysis was appropriate and that it supports treatment for PPMS, especially in those with gadolinium enhancing lesions. The panel considered that the current MR access criteria to demonstrate active disease could be applied for PPMS.

10.3. MSTAC **recommend** funding with a medium priority for PPMS with ocrelizumab, in patients with active inflammatory disease.