Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 12 & 13 November 2020

The records of PTAC and Subcommittees of PTAC 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 meeting; only the relevant portions of the record relating to discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

PTAC and Subcommittees of PTAC 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

PHARMAC is not bound to follow the recommendations made below. Applications are prioritised by PHARMAC against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or PTAC Subcommittees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

Present:

PTAC members:
Mark Weatherall (Chair)
Marius Rademaker (Deputy Chair)
Alan Fraser
Brian Anderson
Elizabeth Dennett
Giles Newton Howes
Jane Thomas
Jennifer Martin
Lisa Stamp
Matthew Strother
Rhiannon Braund
Sean Hanna
Simon Wynn Thomas
Stephen Munn
Tim Stokes

Apologies – PTAC Members:

Bruce King

1. The role of PTAC, PTAC Subcommittees and meeting records

1.1. This meeting record of PTAC is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016, available on the PHARMAC website at https://www.pharmac.govt.nz/assets/ptac-terms-of-reference.pdf.

1.2. The PTAC Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of PTAC and PTAC Subcommittees.

1.3. Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

1.4. PTAC and PTAC Subcommittees have complementary roles, expertise, experience, and perspectives. PTAC may therefore, at times, make recommendations that differ from PTAC Subcommittees', including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC Subcommittees may, at times, make recommendations that differ from PTAC's, or from other PTAC Subcommittees', when considering the same evidence.

1.5. PHARMAC considers the recommendations provided by both PTAC and PTAC Subcommittees when assessing applications.

2. Record of PTAC meetings held August 18 2020 and September 18 2020

2.1. The Committee reviewed the records of the PTAC meetings on August 18 and September 18 2020.

2.2. The Committee accepted the records for both meetings held via video conference on the 18th of August and September.

3. Subcommittee Minutes

Immunisation Subcommittee of PTAC

3.1. The Committee noted the record of the Immunisation Subcommittee of PTAC held on 2 September 2020.

3.2. The Committee noted the Subcommittee advice that influenza seasons are highly variable and seasons when H2N2 circulates are particularly severe for people aged over 65. The Committee noted the Subcommittee advice that, from first principles, an adjuvanted vaccine may address the issue of immunosenescence for older adults.

3.3. The Committee changed its recommendation for an adjuvanted quadrivalent influenza vaccine to Cost Neutral to unadjuvanted quadrivalent influenza vaccine on the basis of the additional expert advice provided by the Immunisation Subcommittee.

4. Correspondence & Matters Arising

4.1. The Committee were presented with correspondence from Janssen in regard to esketamine for treatment-resistant depression.

4.2. The Committee agreed to consider this by email.

5. Esketamine for the treatment of major depressive disorder with active suicidal ideation with intent (MDSI)

Application

5.1. The Committee reviewed the application for esketamine for the treatment of major depressive disorder with active suicidal ideation with intent (MDSI).

5.1.1. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

5.2. The Committee **recommended** that the application for esketamine in the treatment of major depressive disorder with active suicidal ideation with intent (MDSI) be declined due to a lack of clinically relevant benefit and poor generalisability to the New Zealand context.

5.2.1. In making this recommendation, the Committee considered that the definition of 'major depressive disorder with active suicidal ideation with intent' was not validated or found in the psychiatric nosology as a recognised, clinically meaningful, diagnostic category of depression; that esketamine has the potential to cause a substance abuse disorder with impact on patients, family/whānau and children; that the implementation and support of esketamine as proposed would significantly affect health services (including primary care and pharmacy services); and that the poor evidence supporting a clear clinically meaningful benefit would likely result in esketamine having relatively poor cost-effectiveness.

Discussion

5.3. The Committee noted that, in February 2020, PTAC reviewed an application for esketamine for treatment-resistant depression (TRD) and had recommended that the application be declined for a number of reasons including: the poor evidence supporting clear meaningful clinical benefit; evidence that was not directly applicable to the New Zealand setting; the risks of high uptake, potential misuse and diversion; the absence of exit criteria; and uncertainty of long-term dependence and tolerance with esketamine. At that time, PTAC also considered there was a risk that patients with TRD may inappropriately receive esketamine ahead of other suitable treatments or strategies.

5.4. The Committee noted that the supplier had responded to the February 2020 PTAC record regarding the application for esketamine for TRD; the Committee noted that this response would be reviewed and considered outside the current meeting.

5.5. The Committee noted the substantial health need of patients with depression and that mental health issues are the third greatest contributor to disability-adjusted life years lost in New Zealand, with depression the greatest contributor to this loss for women (Ministry of Health, 2016). The Committee noted that depression has a disproportionate impact on people with low socioeconomic status (Ministry of Health. 2018/19). As such, the Committee recognised the need for new treatment options that show clear, sustained improvement for this chronic condition.

5.6. The Committee considered that there are challenges in that definitions of various types of depression (according to clinical guidelines) are difficult to use to strictly define a specific clinical population. The Committee noted that, despite challenges with definitions, the patient population with major depression is a much larger group (and with a lower threshold proposed for eligibility for esketamine) than that previously considered for treatment-resistant depression, and considered that the latter is a subgroup of major depressive disorder. The Committee considered that an accurate and fulsome diagnosis of major depressive disorder could not be done without psychiatric assessment.

5.7. Members considered that a substantial proportion of people with major depressive disorder have some degree of suicidal intent and considered that assessment of active intent would be subjective and inconsistent between clinicians and clinical settings. The Committee noted that the available evidence does not provide a clear or consistent definition of 'major depressive disorder with active suicidal ideation with intent' and that this is not a separate disease entity that is recognised in clinical practice.

5.8. Members considered that, while there is an association between suicidal ideation and completed suicide described in the literature at a population level, the association at an individual level was unclear. Members considered that there is no evidence that individual interventions reduce the population rate of suicide, and that appropriate measures for suicide prevention would likely be public health measures.

5.9. The Committee noted that 20% of the New Zealand population have mental health or substance abuse disorders using lifetime prevalence data (Oakley Browne, 2006). The Committee noted that the lifetime risk of depression in New Zealand is about 16% (Ministry of Health, 2019), equating to about 350,000 people in New Zealand of whom 20-30% have treatment-resistant depression (Rush et al. Am J Psychiatry. 2006;136:1905-17). The Committee noted that greater rates of mental health problems, including suicide are reported in Māori compared with non-Māori.

5.10. The Committee considered that the supplier's patient number estimates were significantly lower than the potentially eligible population. The Committee considered that, with a suicidal ideation rate of a third of all depressed patients, that up to 110,000 people in New Zealand could fit the proposed eligibility criteria for esketamine for the treatment of major depressive disorder with active suicidal ideation with intent.

5.11. The Committee noted that funded treatments for depression were described by PTAC in February 2020 and that no treatments are specifically funded for major depressive disorder with active suicidal ideation, as this is not a specifically defined condition in clinical practice. The Committee noted the current Royal Australian and New Zealand College of Psychiatrists treatment algorithm for patients with moderate to severe major depressive disorder is consistent with treatment of such patients in most developed countries (Malhi et al. Aust N Z J Psychiatry. 2015;49:1087-206).

5.12. Members considered that the patient population described by this application i.e. those with major depressive disorder, would receive usual funded pharmaceutical and other treatment for major depressive disorder, with electroconvulsive therapy (ECT) reserved for the subset of people with very severe treatment-refractory depression (largely in older people). Members considered that a significant proportion of this patient population would be managed by secondary DHB psychiatric services. Members noted that ECT requires administration by an RANZCP-credentialled clinician in a theatre setting, and therefore use is constrained by theatre time and clinician availability. It was considered that it would be used only in patients with longstanding, severe depression or in some acute cases e.g. including patients with catatonic depression, hallucinations and inability to eat or drink. As such, ECT was not considered to be an appropriate comparator, or particularly relevant, for this population.

5.13. The Committee noted that the pharmacological properties and administration (including substantial healthcare resource) of esketamine was described by PTAC in February 2020 and that esketamine has since been approved by Medsafe for the rapid reduction of depressive symptoms in patients with major depressive disorder who have active suicidal ideation with intent. The Committee noted that esketamine is a class 4 controlled drug administered intranasally, with mucosal systemic absorption occurring in about 10 minutes.

5.14. The Committee noted that esketamine is proposed to be used as an adjunctive treatment to achieve rapid reduction of depressive symptoms in patients defined as having major depressive disorder with active suicidal ideation with intent. Administration was for

four weeks with oral antidepressants, and other appropriate therapy, continued as per clinical judgement. The Committee considered it was unclear how esketamine would be appropriately incorporated into the established treatment paradigm from a pragmatic perspective.

5.15. The Committee noted that the 60-point Montgomery-Asberg Depression Rating Scale (MADRS) is often used in trials of treatments for major depressive disorder and also in the trials considered in this application. The Committee noted that different methods have been used to provide different minimum clinically important differences (MCIDs) in MADRS ranging from 1.6 to 1.9 (with statistical distribution methods) to requiring a decrease of about 8-10 points for classification of remission (anchor-based methods). Members considered anchor-based methods of understanding MCID using the MADRS to reflect clinical reality more closely. Members noted that MADRS provides a scale for measurement of depression; but not 'with suicidal ideation' and that the MADRS does not predict who will complete suicide.

5.16. The Committee noted the results of the phase III, double-blind, randomised (1:1), placebo-controlled ASPIRE-1 trial. This included 226 adults aged 18-64 years with a diagnosis of major depressive disorder with active suicidal intent, without psychotic features. They received intranasal esketamine 84 mg plus a new antidepressant (N=114) or intranasal placebo plus a new antidepressant (N=112) for four weeks with follow-up to nine weeks post treatment (Fu et al. J Clin Psychiatry. 2020;81:19m13191). The Committee noted that the trial included patients with mean baseline MADRS of 41.1 and excluded patients with many comorbidities and other problems (e.g. substance abuse) that may exist in the target population.

5.16.1. The Committee considered that ASPIRE-1 was designed as an efficacy trial and noted that the placebo included a bittering agent, however, the Committee considered that the dissociative effect of the active treatment would be obvious compared to placebo and could thus impact the study blinding.

5.16.2. Members considered that extended hospitalisation i.e. 25 days as in some clinical trials, different anti-depressant treatments and psychosocial variables as likely to influence the improvement of major depression.

5.16.3. The Committee noted that the primary outcome of ASPIRE-1 was a decrease in MADRS score at 24 hours, although the trial did not specify a MCID for this outcome, and that the least squares mean difference in MADRS score from baseline to 24 hours was -3.8 (standard error=1.39; 95% CI: -6.56 to -1.09, P=0.006). The Committee noted that the difference in MADRS between groups generally was maintained over time through to the end of follow-up, and considered that it was difficult to gauge the clinical significance of these small differences in MADRS (esketamine vs placebo) at 24 hours and at day 25. The Committee noted there was no statistically significant difference in severity of suicidality at 24 hours.

5.17. The Committee considered that the evidence from ASPIRE-1 was of high quality and generalisable to the New Zealand context, other than the prolonged hospital admissions which were considered significantly different from usual care in New Zealand. The Committee noted the results of the phase III, multi-centre, double-blind, randomised (1:1), placebo-controlled ASPIRE-2 trial. This occurred in 230 adults aged 18-64 years with major depressive disorder and active suicidal ideation. They received twice-weekly esketamine (84 mg intranasal) plus standard of care or intranasal placebo plus standard of care for four weeks (Ionescu et al. Eur Neuropsychopharmacol. 2019;29(Suppl 6):S414-5; Ionescu et al. Int J Neuropsychopharmacol. 2020; DOI: 10.1093/ijnp/pyaa068 [Epub ahead of print]). The Committee noted that participants saw an emergency department doctor, agreed to participate in the trial and were admitted to hospital (mean 22 days). The Committee noted that participants self-administered questionnaires after 24 hours describing their symptoms.

5.17.1. The Committee noted that ASPIRE-2 participants had a mean baseline MADRS of 39.7 and could receive up to 6 mg of lorazepam daily. The Committee considered it was unclear how many participants received benzodiazepines, which could substantially impact a patient's affective state at the primary end point.

5.17.2. Members considered that the trial's exclusion criteria would have excluded a substantial proportion of the New Zealand patient population being treated on psychiatric wards for major depressive disorders.

5.17.3. The Committee noted that some antidepressants used in ASPIRE-2 e.g. duloxetine, are not funded for use in New Zealand for treatment of depression, which the Committee considered limited the applicability of this evidence to the New Zealand population. The Committee also considered that the time frame for hospital admission (mean 22 days) significant limited generalisability to the New Zealand context.

5.17.4. The Committee noted that the primary outcome was assessed at four hours after the first dose, when patients would still be dissociated, and that missing data was imputed with the last observation carried forward (LOCF) method. Although it was unclear how many datapoints were affected by LOCF, the Committee considered this could potentially pose a significant bias.

5.17.5. The Committee noted that the ASPIRE-2 trial specified an MCID of 6 for the MADRS. The Committee noted that the least squares mean difference change in MADRS total score from baseline to 24 hours was -3.9 (95% CI: -6.60 to -1.11, P=0.006); a difference of 3.3 in mean MADRS score was reported, with mean decrease in MADRS of -15.7 with esketamine compared with -12.4 with placebo (Ionescu et al. 2020), however, the Committee noted that results at all other timepoints were not statistically significant and considered these results were not clinically meaningful. The Committee noted that the trial reported no statistically significant difference in suicidality score between groups.

5.18. The Committee noted the results of the phase II, multi-centre, double-blind, randomised, placebo-controlled PERSEVERE trial. This included 68 adults aged 19-64 with major depressive disorder at imminent risk of suicide who received twice-weekly esketamine (84 mg intranasally) or placebo for four weeks, with eight weeks of follow-up (Canuso et al. Am J Psychiatry. 2018;175:620-30). Members noted that participants received trial treatment within inpatient psychiatric units in the US, and considered the healthcare and duration of hospital stay would be different to that of New Zealand.

5.18.1. Members considered that patients in PERSEVERE had less severe depression at baseline compared to ASPIRE-1 and ASPIRE-2 participants. The Committee noted that the trial was powered for a MCID mean change in MADRS of 6, and also measured for suicidal ideation, rather than suicide.

5.18.2. The Committee noted that there was a statistically significant difference in MADRS at 24 hours (least squares mean difference in MADRS from baseline to 24 hours post-treatment was -7.2 (± SE 2.85, P=0.015); effect size 0.65. The Committee noted this separation between groups disappeared by 25 days (least squares mean difference in MADRS from baseline to four weeks post-treatment was -4.5, (± SE 3.14, P=0.159); effect size 0.35. The Committee noted that there was no difference in suicidality between groups and that there was no statistically significant improvement in MADRS at eight weeks, which was the primary study endpoint.

5.18.3. The Committee considered that PERSEVERE participants appeared to benefit from the addition of another antidepressant and four weeks of hospital care while on the trial. Members considered that the known dissociative effect of esketamine

likely provided some brief relief from depression, although this was not clearly long-term.

5.19. The Committee noted that the toxicity profile of esketamine included dizziness, dissociation, nausea, cognitive impairment and transient blood pressure increases that could be a significant issue for people with cardiovascular disease or severe hypertension. The Committee noted that esketamine is contraindicated with patients with cardiovascular risk factors (Medsafe Data Sheet, 2019). Members considered that patients with pre-existing substance abuse issues may experience detrimental effects from esketamine dosing and that medicine interactions e.g. those taken for pain or depression, could occur.

5.20. The Committee noted the results of a pooled analysis of data from 456 patients from ASPIRE-1 and ASPIRE-2, which reported a least squares mean difference for change in baseline MADRS score at 4 hours post treatment of -3.8 (95% CI: -5.75 to -1.89) and reported no statistically significant difference in severity of suicidality between groups (Canuso et al. Neuropsychopharmacology. 2019;44:385–538. Abstract W130. https://doi.org/10.1038/s41386-019-0547-9)

5.21. The Committee considered that the clinical trials provided high quality evidence of a statistically significant difference in MADRS at 24-hours; no difference in MADRS at 25 days; and no difference in suicidal intent. The Committee noted the trials did not consistently show a mean difference in MARDS close to the MCID in their primary end points. The Committee noted that the trials did not include outcomes regarding suicide and therefore could not inform whether the intervention changed the suicide rate within the trial patient groups; noting that different outcomes would be needed to study suicide prevention on a population level. Overall, the Committee considered that there was a lack of a clinically relevant benefit and poor generalisability to New Zealand population.

5.22. The Committee noted that major depressive disorder is of at least two weeks duration by definition and considered that an improvement of only 24-hours is unlikely to convey benefits to family/whānau or wider society.

5.23. The Committee considered that there is an addiction risk with esketamine and that esketamine has the potential to cause a substance abuse disorder, with impacts on patients, family/whānau and children. The Committee considered that the supplier's Risk Mitigation Plan did not provide enough detail on how this risk would be managed and left a significant degree of uncertainty as to use of product in the New Zealand context.

5.24. The Committee considered it was unclear who would provide and dispose of the metered dose nasal spray pumps, and members considered that the disposal of a large number of single-use devices would be a potential environmental concern.

5.25. The Committee considered that in order to provide treatment with esketamine, patients should be admitted to hospital, and considered that it was unclear how this would be managed, noting that clinical trial participants may have stayed in hospital for a longer period than for current standard care in New Zealand (~10 days).

5.26. The Committee noted that administration, implementation and support of esketamine as proposed would require substantial service provision; would significantly impact health services including primary healthcare services; and would require substantial upfront and ongoing costs for treatment facilities, staff and patient monitoring. Members considered that patients should see a psychiatrist in person for assessment prior to being prescribed esketamine. The Committee considered that any accessibility issues would have the potential to increase access inequities.

5.27. The Committee noted that the Special Authority criteria proposed by the supplier for esketamine for the treatment of patients defined as having major depressive disorder with active suicidal ideation with intent did not require a patient to have treatment-resistant depression or be hospitalised; required a need for rapid relief; and excluded several related

disorders e.g. addiction and dependency. The Committee considered that the criteria as proposed could not be implemented consistently or easily in the New Zealand setting to target funded treatment appropriately to those with severe depression, and that it would potentially discriminate against patients at need e.g. those with addiction/dependency. The Committee noted that the proposed Special Authority criteria did not include stopping rules, observation requirements, appropriate dispensing, or renewal criteria; many of which would be required to appropriately target funded treatment.

5.28. The Committee considered that uptake of esketamine would likely be influenced by marketing and resources available for treatment. Members considered that if esketamine were funded, it may also be appealing to patients with other conditions comorbid with depression and their prescribers, increasing the risk of 'slippage' of funded treatment.

5.29. The Committee considered that health utility would be required to be incorporated into economic modelling, and that data for prevention or completion of suicide was not available. The Committee considered that the evidence for MADRS was not associated with suicidality. Members considered that ECT would not be a comparator treatment for modelling purposes in this patient population, and that esketamine would be used in combination with other antidepressants and benzodiazepines. The Committee considered that the availability of esketamine would be unlikely to change the use of ECT, which occurs at a low rate in a subset of high need patients.

5.30. Overall, the Committee considered that despite the high health need of this patient population, the evidence did not indicate that esketamine would provide a clinically meaningful benefit for patients with major depressive disorder with active suicidal ideation, and considered that esketamine would be associated with a number of possible risks and impacts for patients, their families/whānau, wider society and the health system.

5.31. Members considered that a majority of the concerns raised in February 2020 by the Committee in regard to the application for esketamine for treatment-resistant depression remained applicable for this application in the broader population described as having major depressive disorder with active suicidal ideation, although noted that the supplier's correspondence regarding the February 2020 record would be reviewed outside of this meeting.

6. Ocrelizumab for the treatment of primary progressive multiple sclerosis (PPMS)

Application

6.1. The Committee reviewed the resubmission from Roche for ocrelizumab for the treatment of primary progressive multiple sclerosis (PPMS)

6.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

6.3. The Committee **recommended** that ocrelizumab for the treatment of primary progressive multiple sclerosis (PPMS) be listed with a **low priority**.

6.4. The Committee made this recommendation based on the high health need of people with PPMS, lack of funded treatment options and modest evidence of benefit of ocrelizumab for this indication, as reported in an extension study.

6.5. In making this recommendation, the Committee considered that PHARMAC could seek advice from the Neurological Subcommittee and/or Multiple Sclerosis Treatments Advisory Committee (MSTAC) on the following points:

- Clinically appropriate EDSS scores for Special Authority treatment initiation and renewal criteria;

- The appropriateness of the 2010 McDonald criteria as part of the entry criteria; and
- The role of MRI in diagnosis and management of PPMS.

6.6. The Committee noted it could revisit this recommendation following advice on the above points by the Neurological Subcommittee and/or MSTAC.

Discussion

6.7. The Committee noted a resubmission from Roche for the use of ocrelizumab for the treatment of PPMS.

6.8. The Committee noted that a funding application for ocrelizumab for the treatment of PPMS was reviewed and recommended for decline by PTAC in February 2018. The Committee noted that at the time, it was considered that despite the high unmet health need in people with PPMS, there were significant concerns with the application, including a lack of data to establish both the safety and efficacy in this currently untreated group, and PTAC considered that the pivotal study (ORATORIO – Montalban et al. N Engl J Med. 2017;376(3):209-20) that was reviewed may have had a bias in the estimate of effectiveness. The Committee noted at the time that more studies were ongoing, and likely to be completed and published in the near future, which may address some of these concerns.

6.9. The Committee noted that in June 2018, advice was sought from the Multiple Sclerosis Treatments Advisory Committee (MSTAC), which recommended that ocrelizumab be funded with a medium priority for PPMS with active inflammatory disease. PTAC noted that MSTAC had in turn noted that the ORATORIO trial population composition was unusual, with 25% having MR gadolinium enhancing lesions; however, MSTAC had considered that the trial publication's statistical analysis was appropriate and that it supported treatment for PPMS, particularly in those with gadolinium enhancing lesions. The Committee noted that in November 2018, PTAC noted MSTAC's recommendation, but still considered that more robust evidence of improved health outcomes was needed to change PTAC's previous recommendation that the application be declined.

6.10. The Committee noted that ocrelizumab has been funded since December 2019 for relapsing-remitting multiple sclerosis (RRMS) subject to Special Authority criteria, and that all applications are currently assessed by the MSTAC.

6.11. 9.12. The Committee noted that multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) caused by dysregulation of the peripheral immune system and leading to demyelination of neurons and subsequent neurodegeneration. The Committee noted that the majority (85-90%) of MS patients are diagnosed with relapsing remitting MS (RRMS). Some of these patients may later develop into secondary progressive MS (SPMS). The remaining 10-15% of patients with MS are diagnosed with PPMS. Some data suggests that 12% of the NZ MS population has PPMS. The Committee noted that diagnosis of PPMS is often retrospective, and that patients often present with significant disability. The Committee noted that rates for PPMS are similar between men and women, whereas RRMS is more common in women.

6.12. The Committee noted that differentiating between PPMS and RRMS can be difficult, as it is not always clear where an individual patient falls on the spectrum of disease, and diagnostic tools for MS such as imaging methods and biomarkers aren't well established. The Committee noted that MS is a multifactorial disease, not simply a chronic inflammatory process, and that PPMS has similar pathophysiological features to SPMS. The Committee noted that current disease management costs associated with RRMS are higher than that of PPMS, as there are multiple targeted disease-modifying treatments available for RRMS and none for PPMS.

6.13. The Committee noted that ocrelizumab is a recombinant humanised monoclonal antibody that selectively targets B-cell expressing CD20 cells. The Committee noted that ocrelizumab is Medsafe approved, however the precise mechanism of action is not fully elucidated. The Committee noted that the PBAC (Australia) recommended ocrelizumab be declined for funding for the treatment of PPMS, but that it was recommended for funding by the CADTH (Canada), SMC (Scotland) and NICE (UK/Wales).

6.14. The Committee noted the Special Authority access criteria for ocrelizumab proposed by the supplier for the treatment of PPMS included initiation at an Expanded Disability Status Scale (EDSS) score of 2.0 (minimal disability in one functional system) to 6.5 (constant bilateral assistance (canes, crutches, or braces) required to walk about 20 metres without resting); with patients able to remain on treatment until they reach EDSS 8.5 (essentially restricted to bed much of the day, some effective use of arm(s), retains some self-care functions). The Committee noted that in the original application submitted for ocrelizumab for PPMS, the proposed stopping criteria had been EDSS 7.0. The Committee noted that under the proposed Special Authority, diagnosis of MS would require MRI confirmation, and a diagnosis of PPMS under the revised 2010 McDonald criteria, which includes both clinical progression scoring and cerebrospinal fluid abnormalities.

6.15. The Committee considered that the most appropriate comparator to ocrelizumab for PPMS was best supportive care, as there are no targeted treatments currently funded for this patient population. The Committee considered that the proposed outcome of reduction in the rate of disease progression as measured by EDSS score was appropriate, however that the role of MRI in measuring treatment outcomes was unclear. The Committee noted that ocrelizumab would be used in combination with intravenous methylprednisolone 100 mg as a pre-infusion, with optional prophylaxis with analgesics or antipyretics and antihistamines pre-infusion as per the ORATORIO trial protocol.

6.16. The Committee noted that the primary results of the ORATORIO phase III, randomised (2:1), double-blind, parallel group, multicentre trial were reviewed by PTAC in 2018 (Montalban et al, N Eng J Med 2017;376:209-20). The Committee noted a long-term open-label extension of the ORATORIO trial (Wolinsky et al. Lancet Neurol. 2020;19:998-1009) was included as part of the resubmission. The Committee noted that, according to trial protocol, blinded treatment in the trial continued until a benefit-risk assessment, at which point the patient allocation was unblinded. The Committee noted that patients were followed for at least 6.5 years, with 3.5 years in the open-label extension phase of the study, and that all analyses were post-hoc.

6.16.1. The Committee noted in long-term follow up evidence that patients in the ORATORIO study underwent a benefit-risk assessment at 144 weeks, at which point patients could cross-over from placebo to ocrelizumab. The Committee noted that the cross-over period was approximately 96 weeks. The Committee considered that the cross-over design produced results which indicated outcomes of delaying ocrelizumab treatment by possibly two years.

6.16.2. The Committee noted that the results of the ORATORIO open-label extension trial indicate that treatment with ocrelizumab from the beginning of the trial suggested a decrease in disability progression (as determined by EDSS score) when compared with patients treated with placebo who crossed-over to ocrelizumab (HR 0.72, 95% CI 0.58 to 0.89, p=0.0021). The Committee noted that the proportion of patients with EDSS ≥7 was lower in the ocrelizumab treatment group compared with the placebo/ocrelizumab group (HR 0.58, 95% CI 0.38 to 0.89, p=0.0112). The Committee noted that there were no new safety signals identified.

6.17. The Committee noted that disability from PPMS occurs twice as fast as in RRMS, with a median time to requiring a walking aid (EDSS 6) of 8-9 years, and median time to wheelchair use (EDSS 7) less than 20 years (Correale et al. Brain. 2017;140:527-46). The Committee considered that the follow-up time of 6.5 years for the ORATORIO study was

too short for what is a slow progressing disease such as PPMS and suggested that a 15-year follow-up would have been more appropriate.

6.18. The Committee noted that the ORATORIO study used the Timed 25-Foot Walk (T25FW) Test and the 9-Hole Peg Test (9HPT) as measures of PPMS progression. The Committee noted that PPMS is a heterogeneous disease and that some patients may have lower limb disability without upper limb disability and vice versa; as such the Committee considered that the two tests may not be clinically meaningful descriptors of progression for all patients. The Committee noted that the proportion of patients having confirmed disability progression as per the T25FW test and the 9PHT was less in the ocrelizumab group compared with the placebo/crossover group (HR 0.77, 95% CI 0.64 to 0.94 and HR 0.65, 95% CI 0.35 to 0.86, respectively).

6.19. The Committee noted that there was no control group in the open-label extension phase of the trial, and that therefore there was potential for incorrect interpretation and reporting bias. The Committee also noted that there was no subgroup analysis of EDSS scores at the initiation of the study. The Committee noted that because most of the attrition and patient dropout in the trial occurred earlier in the double-blinded phase, this could lead to immortal time bias (ie. survival treatment selection bias) in favour of ocrelizumab and distort the generalisability of results.

6.20. The Committee considered that the evidence from ORATORIO open-label extension study for the use of ocrelizumab in the treatment of PPMS was weak and of low quality, primarily due to the lack of a control arm in the study. The Committee also noted that there was no health-related quality of life data reported, however that there is a well-known relationship between EDSS score and utility, thus quality of life scores can be surmised via EDSS score.

6.21. The Committee considered that the patient number estimates of 265 patients per year for the first three years was appropriate. The Committee noted that there were no subgroup analyses in the ORATORIO study and considered that it was unclear if patients starting on ocrelizumab with a lower EDSS score would benefit more than those initiating treatment with a higher EDSS score. The Committee also considered that a stopping criterion of an EDSS score of 8.5 seemed high and was perhaps too far into disease progression for ocrelizumab to have appreciable benefit. The Committee considered that PHARMAC could seek advice from the Neurological Subcommittee and/or MSTAC on appropriate EDSS scores, and other starting and stopping criteria for ocrelizumab for the treatment of PPMS. The Committee also considered that it would be beneficial to assess a cost-utility analysis comparing patients with low EDSS scores at onset (3 or lower) to patients with higher EDSS scores (4 or over) when initiating ocrelizumab.

6.22. The Committee also noted that it was unclear on the role of MRI surveillance throughout the treatment process, noting that MRI assessment was part of the protocol for surveillance in the ORATORIO study, which may not be practical in the New Zealand clinical setting, and considered PHARMAC could seek advice from the Neurological Subcommittee and/or MSTAC on the role of MRI in MS treatment in this context.

6.23. The Committee noted that the supplier had provided an economic model with the assumption that median age for starting treatment on ocrelizumab would be 40 years old. The Committee noted that the median age in the ORATORIO study was 46, with a range of 18 to 56 years. The Committee was unclear if an addition of six years would make a difference to the modelling results and suggested that PHARMAC staff investigate this. The Committee also noted that the economic modelling included a relative risk of death for patients with MS set 2.89 times that of the expected age-normative probability of death in New Zealand, based on the reported standardised mortality ratio reported in a Canadian observational study, which was used in the PPMS specific model. (Kingwell et al. J Neurol Neurosurg Psychiatry. 2012;83:61-6). The Committee noted that PPMS had higher relative mortality risk compared to RRMS (relative mortality ratio 1.52; 95% CI 1.30 to 1.80), which

should be factored into any economic modelling to further differentiate the health needs of patients with PPMS from RRMS.

6.24. The Committee noted that the McDonald criteria are used for diagnosis of PPMS, and that one of the PPMS criteria is continued progression for one year (from previous symptoms or by ongoing observation). The Committee noted that waiting 12 months for a diagnosis may mean that patients with EDSS scores of 0 or 1 will progress to higher EDSS scores without having any funded treatment options. The Committee considered that PHARMAC could seek advice from the Neurological Subcommittee and/or MSTAC on the appropriateness of waiting 12 months to initiate ocrelizumab treatment.

6.25. The Committee noted that the discontinuation rate in the ORATORIO study was 31% over the 6.5-year follow-up period (126 patients in the double-blinded phase, and 22 patients in the open-label extension phase). The Committee considered that the discontinuation rate was appropriate to inform PHARMAC's budget impact analysis. The Committee considered that, if funded, the uptake rate of ocrelizumab for PPMS would likely be 100%, as there are currently no alternative targeted treatments.

6.26. The Committee again noted the high health need of people with PPMS, the lack of funded treatment options and modest evidence of benefit of ocrelizumab for this indication, as demonstrated in a low-quality extension study. The Committee considered that PHARMAC could seek advice from the Neurological Subcommittee and/or the MSTAC on appropriate Special Authority criteria.

7. Atezolizumab in combination with nab-paclitaxel for the treatment of unresectable locally-advanced or metastatic triple-negative breast cancer

Application

7.1. The Committee reviewed the application for atezolizumab in combination with nab-paclitaxel for the treatment of unresectable locally-advanced or metastatic triple-negative breast cancer.

7.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

7.3. The Committee **recommended** that the application for atezolizumab in combination with nab-paclitaxel for the treatment of unresectable locally-advanced or metastatic triple-negative breast cancer be **declined**, due to evidence of a lack of overall survival benefit (compared with placebo plus nab-paclitaxel) in a key clinical trial and limitations of the PD-L1 positive subgroup analysis.

7.3.1. In making this recommendation, the Committee considered the high unmet health need of patients with triple-negative breast cancer including the lack of effective funded treatment options for triple-negative breast cancer; the novel approach of immune checkpoint inhibitor treatment in combination with chemotherapy for triple-negative breast cancer; the challenges associated with PD-L1 testing in New Zealand; the limited relevance of the treatment regimen (including nab-paclitaxel) to the New Zealand patient population; and the lack of quality of life data, which affected the ability of the Committee to assess of the supplier's therapeutic claims.

7.4. The Committee suggested that CaTSoP's advice be sought, including advice on: the use of paclitaxel instead of nab-paclitaxel with atezolizumab in this indication; the treatment paradigm for patients with triple-negative breast cancer in New Zealand; the impact paclitaxel and corticosteroid premedication may have on immunotherapy activity; the results of the IMpassion131 trial; and patient number estimates for atezolizumab in this setting.

Discussion

7.5. The Committee noted that breast cancer is a leading cause of cancer-related death in New Zealand (Seneviratne et al. Cancer Causes Control. 2015;26:1813-24).

7.6. The Committee noted that triple-negative breast cancer is diagnosed when breast tumours have little or no expression of all of: oestrogen receptors, progesterone receptors, or human epidermal growth factor receptor-2 (HER2). The Committee considered that triple-negative breast cancer is an aggressive form of breast cancer that accounts for 15-20% of all breast cancer diagnoses, is typically associated with earlier age of onset and has a worse prognosis than other breast cancer subtypes (Lawrenson et al. N Z Med J. 2018;131:51-60).

7.7. The Committee noted that although breast cancer disproportionately affects Māori with higher incidence and mortality rates than non-Māori, triple-negative breast cancer is less common in Māori women and in Pacific women than non-Māori and non-Pacific women (Lawrenson et al. 2018).

7.8. The Committee considered that patients with locally advanced or metastatic triple-negative breast cancer generally receive multiple lines of chemotherapy, typically using sequential single agent therapy with a taxane (docetaxel, paclitaxel) or anthracycline (doxorubicin, epirubicin) for advanced or metastatic disease, if not previously used as adjuvant therapy. Members considered that some younger patients may be suitable candidates for a multi-agent chemotherapy regimen, however, the combination of cyclophosphamide and doxorubicin would only be used in rare cases due to its known toxicity profile. The Committee considered that CaTSoP may be able to provide further advice on the treatment paradigm for patients with triple-negative breast cancer.

7.9. The Committee noted that nanoparticle albumin-bound (nab)-paclitaxel is not currently funded in New Zealand, however, several funding applications have been considered by PTAC and CaTSoP; most recently in May 2019, PTAC reiterated its previous recommendation to fund nab-paclitaxel for all types of metastatic breast cancer only if cost-neutral to weekly paclitaxel after taking into account pharmaceutical and administration costs.

7.10. The Committee noted that there are no targeted therapies specifically for triple-negative breast cancer, due to the lack of receptor positivity, and considered that internationally these patients have limited effective treatments and a high unmet health need that has not improved over recent decades.

7.11. The Committee noted that triple-negative breast cancers are considered likely to respond well to immunotherapy, due to high levels of tumour-infiltrating lymphocytes, high expression of PD-L1 on tumour and immune cells and high numbers of nonsynonymous mutations; however, efficacy with immunotherapy alone is low, providing a rationale for clinical trials investigating immunotherapy in combination with chemotherapy for triple-negative breast cancer (Keenan et al. J Natl Compr Canc Netw. 2020;18:479-89).

7.12. The Committee noted that the application was for atezolizumab in combination with nab-paclitaxel for unresectable locally-advanced or metastatic triple-negative breast cancer, with PD-L1 expression ≥1% in patients who have not received chemotherapy for metastatic disease, and noted that this indication is approved by Medsafe. The Committee noted that a PD-L1 test is required prior to treatment with atezolizumab and that the supplier has proposed atezolizumab sits in the treatment paradigm ahead of single-agent chemotherapy for patients with PD-L1 positive disease.

7.12.1. The Committee noted that atezolizumab has been considered by PHARMAC for other cancers including urothelial carcinoma and non-small cell lung cancers, however, it is not currently funded in New Zealand for any indication. The Committee noted that PHARMAC has not previously considered atezolizumab for

breast cancer and that this is the first immune checkpoint inhibitor funding application PHARMAC has received for breast cancer.

7.12.2. The Committee noted that the key evidence for atezolizumab in combination with nab-paclitaxel comes from the multi-centre, phase III, randomised (1:1), placebo-controlled, double-blind IMpassion130 trial of 451 patients with untreated locally-advanced or metastatic triple-negative breast cancer (Schmid et al. N Engl J Med. 2018;379:2108-21; Schmid et al. Lancet Oncol. 2020;21:44-59). The Committee noted that the primary outcomes were investigator-assessed progression-free survival (PFS) and overall survival (OS) in both the overall population and PD-L1 positive (tumour infiltrating immune cells [IC] ≥1%) subgroup (N=369, 40.9%), tested hierarchically, and that PD-L1 expression was tested by Ventana SP142 assay, but participant randomisation was not stratified by PD-L1 expression.

7.12.3. The Committee noted that patients in IMpassion130 received first-line treatment with atezolizumab 840 mg or matching placebo intravenously on day 1 and day 15 of every 28-day cycle and nab-paclitaxel 100 mg/m^2 of body surface area intravenously on days 1, 8, and 15 until progression (RECIST 1.1) or unacceptable toxicity. The Committee noted that nab-paclitaxel was used in the trial instead of paclitaxel and noted that treatment protocols for paclitaxel use also include pre-treatment with corticosteroids.

7.12.4. The Committee noted that more than half of IMpassion130 participants previously received treatment with a taxane, ~90% had metastatic disease, and the majority were White (~68%) with a proportion of Asian participants (~20%) and smaller representation from other ethnic groups. The Committee noted that the median time from last surgery until diagnosis of unresectable locally advanced/metastatic disease was 24.5 months with atezolizumab plus nab-paclitaxel and 24.8 months with placebo plus nab-paclitaxel in the intention-to-treat (ITT) population, and 21.5 months and 22.1 months, respectively, in the PD-L1 positive population (Schmid et al. 2020).

7.12.5. The Committee noted that median PFS in the IMpassion130 ITT population was 7.2 months with atezolizumab vs 5.5 months with placebo (stratified hazard ratio [HR] 0.80, 95% CI 0.69 to 0.92, P=0.0025), and considered that although this was statistically significant, the difference in point estimates of median PFS of 1.7 months may not be clinically significant. The Committee noted that the difference in median PFS in the PD-L1 positive subgroup was slightly greater (7.5 months atezolizumab vs 5.0 months placebo, 2.5 months difference; stratified HR 0.62, 95% CI 0.49 to 0.78, P<0.0001; Schmid et al. 2018).

7.12.6. The Committee noted the results of the second interim analysis performed after median follow-up of 18.5 months with atezolizumab and 17.5 months with placebo, which reported median OS of 21.0 months vs 18.7 months, respectively, in the ITT population, which was not statistically significant (stratified HR 0.86, 95% CI: 0.72 to 1.02, P=0.078). The Subcommittee noted the exploratory OS analysis in the PD-L1 positive subgroup with median OS of 25.0 months with atezolizumab vs 18.0 months with placebo; a difference of 7 months (stratified HR 0.71, 95% CI: 0.54 to 0.94; Schmid et al. 2020).

7.12.7. The Committee noted the Kaplan-Meier curves for OS in the ITT population and in the PD-L1 positive and negative subgroups for patients who received atezolizumab with nab-paclitaxel vs placebo with nab-paclitaxel, which crossed over at about 33 months (although fewer than 15% of participants remained). The Committee considered that these analyses were to establish differences in OS over time between groups and treatments.

7.12.8. The Committee noted that IMpassion130 subgroup analysis of OS in PD-L1 positive patients suggested that patients without brain metastases and patients

with bone metastases may have had better outcomes with atezolizumab and nab-paclitaxel than with placebo and nab-paclitaxel, however, these subgroup analyses were post-hoc and exploratory without reporting statistical heterogeneity; it was unclear whether patients with liver metastases received any apparent benefit with atezolizumab (with the 95% confidence interval for the HR crossing 1).

7.12.9. The Committee was made aware of recently-released preliminary reporting of the final IMpassion130 OS analysis (performed after median follow-up of 18.8 months) presented as a conference abstract, which reported a larger relative improvement in median OS with atezolizumab and nab-paclitaxel in the PD-L1 positive subgroup than occurred in the overall trial study population, but this subgroup result had not been formally tested per a prespecified testing hierarchy (Emens et al. Ann Oncol. 2020; 31 Suppl 4:S1148).

7.12.10. The Committee noted that grade 3 or 4 adverse events were reported in about half of IMpassion130 participants (49% atezolizumab plus nab-paclitaxel vs 43% placebo plus nab-paclitaxel) and the most common of these were neutropenia (8% in each group), peripheral neuropathy (6% atezolizumab plus nab-paclitaxel vs 3% placebo plus nab-paclitaxel), decreased neutrophil count (5% vs 4%, respectively) and fatigue (4% vs 3%, respectively). The Subcommittee noted that two deaths were reported in patients who received atezolizumab plus nab-paclitaxel (autoimmune hepatitis related to atezolizumab, and septic shock related to nab-paclitaxel) and one in a patient who received placebo plus nab-paclitaxel (hepatic failure). The Committee considered that in general, the reported safety profile of these treatments in the trial was as expected.

7.12.11. The Committee noted the publication of patient-reported outcomes (PROs) from the IMpassion130 trial, which reported no between-group differences in median time to deterioration (TTD) or in clinically meaningful symptoms (Adams et al. Ann Oncol. 2020;31:582-9). The Committee noted that mean PRO values at specific time-points e.g. baseline; were not reported by randomised group or by PD-L1 subgroup, and considered that the lack of access to the detailed data hindered the Committee's assessment of the supplier's claims regarding the quality of life impact of the proposed regimen.

7.12.12. The Committee considered that IMpassion130 was a good quality phase III trial, however, the results as presented to date did not demonstrate a clear, sufficient benefit from atezolizumab with nab-paclitaxel in the trial population. The Committee noted that P-values were not reported for the subgroup analyses and considered that the post-hoc high PD-L1 expression subgroup analysis and multiple statistical comparisons (needing greater efforts to prevent false positive results) likely led to the trial's negative results.

7.13. The Committee was made aware of a conference abstract providing other relevant evidence for atezolizumab in this patient population from the ongoing, phase III, randomised (2:1), double-blind, placebo-controlled IMpassion131 trial investigating first-line atezolizumab with paclitaxel vs paclitaxel alone in 651 patients with triple-negative breast cancer who received treatment until progression or unacceptable toxicity (Miles et al. Ann Oncol. 2020;31 Suppl 4:S1147-8).

7.13.1. The Committee noted with IMpassion131 that the primary endpoint was investigator-assessed PFS, tested hierarchically in the PD-L1 positive (IC ≥1%) subgroup and then in the ITT population, and that OS and overall response rates were secondary endpoints.

7.13.2. The Committee noted that IMpassion131 stratified patients according to PD-L1 status (by Ventana SP142 assay; 45% of patients being PD-L1 positive), prior taxane use, liver metastases and geographic region. The Committee considered

that use of atezolizumab in combination with paclitaxel, which is a funded treatment option for this patient population in New Zealand (compared with nab-paclitaxel, as in IMpassion130) was more relevant to the New Zealand treatment paradigm.

7.13.3. The Committee noted that the primary results of IMpassion131 to date had reported that atezolizumab with paclitaxel did not improve PFS or OS in either the PD-L1 positive (IC ≥1%) subgroup or in the ITT population (tested hierarchically in that sequence), but that the data to date were preliminary and confined to a conference abstract.

7.14. Overall, the Committee reiterated that the evidence for atezolizumab in triple-negative breast cancer did not yet include a formal analysis of final OS from the IMpassion130 trial; only primary results from IMpassion131 were available, and in abstract form (not a peer-reviewed journal publication); and quality of life data was not provided to inform the Committee's assessment of the supplier's claim regarding the time to deterioration of symptoms. The Committee noted that no data was available for atezolizumab monotherapy in this setting.

7.15. The Committee noted that atezolizumab with nab-paclitaxel for triple-negative breast cancer with >1% PD-L1 expression was recommended for funding by NICE (England/Wales), however, a funding application for atezolizumab with taxane chemotherapy for triple-negative breast cancer was not recommended by the PBAC (Australia) due to limited applicability of the clinical trial evidence for atezolizumab in combination with nab-paclitaxel, as nab-paclitaxel is not funded in Australia, and the uncertain magnitude of an overall survival benefit.

7.16. The Committee considered that the appropriate location of the proposed regimen within the New Zealand treatment paradigm was unclear. The Committee considered that paclitaxel would be used in New Zealand instead, although noted that paclitaxel requires corticosteroid premedication which is hypothesised to affect immunotherapy activity (Schmid et al. 2018) and that use in combination with paclitaxel is not a Medsafe-approved indication.

7.17. The Committee considered that the supplier's estimate of eligible patient numbers, 74 incident patients a year before uptake, was reasonable given the likely young age of patients with triple-negative breast cancer but sought further advice from CaTSoP on this.

7.18. The Committee considered it unclear what impact atezolizumab for triple-negative breast cancer would have on healthcare costs associated with managing toxicities, and considered that the frequent (albeit, short) infusions would impact on healthcare services. The Committee noted that funding atezolizumab in this indication would incur significant costs to enable PD-L1 testing e.g. for training and quality control, and noted that the Ventana assay is not routinely used in New Zealand.

7.19. The Committee considered that atezolizumab was a high-cost medicine that is proposed to be used prior to other lines of therapy, therefore resulting in a high cost to the pharmaceutical budget. The Committee considered that, if atezolizumab were funded for this indication, nab-paclitaxel would need to be funded for this indication.

7.20. Given the concerns regarding the overall survival benefit in the ITT population and in the PD-L1 positive subgroup (and noting the high health need of this patient population; the challenges associated with PD-L1 testing in New Zealand; the low relevance of the treatment regimen (including nab-paclitaxel) to the New Zealand patient population; and the lack of quality of life data, which limited the Committee's assessment of the supplier's therapeutic claims), the Committee did not support funding of atezolizumab with nab-paclitaxel for triple-negative breast cancer in New Zealand.

7.21. The Committee suggested that CaTSoP's advice be sought , including advice on: the use of paclitaxel instead of nab-paclitaxel with atezolizumab in this indication; the treatment paradigm for patients with triple-negative breast cancer in New Zealand; the impact paclitaxel and corticosteroid premedication may have on immunotherapy activity; the results of the IMpassion131 trial; and patient number estimates for atezolizumab in this setting.

8. Vedolizumab for the treatment of Crohn's disease and ulcerative colitis

Application

8.1. The Committee reviewed the application from the New Zealand Society of Gastroenterology (NZSG) for vedolizumab for the treatment of patients with Crohn's disease (CD) who have either had failure of, became refractory to, or experienced severe and intractable side effects from infliximab and/or adalimumab.

8.2. The Committee reviewed the application from the New Zealand Society of Gastroenterology (NZSG) for vedolizumab for the treatment of patients with ulcerative colitis (UC) who have either had failure of, or became refractory to, or experienced severe and intractable side effects from infliximab.

8.3. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

8.4. The Committee **recommended** that vedolizumab be listed as a first line biologic treatment for Crohn's disease if cost neutral to TNF-α inhibitors, subject to the following Special Authority criteria:

Initiation – Crohn's disease (adults)
Applications only from a gastroenterologist or Practitioner on the recommendation of a gastroenterologist. Approvals valid for 4 months.

All of the following:
1 Patient has severe active Crohn's disease; and
2 Any of the following:
2.1 Patient has a Crohn's Disease Activity Index (CDAI) score of greater than or equal to 300; or
2.2 Patient has extensive small intestine disease affecting more than 50 cm of the small intestine; or
2.3 Patient has evidence of short gut syndrome or would be at risk of short gut syndrome with further bowel resection; or
2.4 Patient has an ileostomy or colostomy, and has intestinal inflammation; and
3 Patient has tried but had an inadequate response to, or has experienced intolerable side effects from, prior systemic therapy with immunomodulators at maximum tolerated doses (unless contraindicated) and corticosteroids; and
4 Surgery (or further surgery) is considered to be clinically inappropriate.

Initiation – Crohn's disease (children)
Applications only from a gastroenterologist or Practitioner on the recommendation of a gastroenterologist. Approvals valid for 4 months.

All of the following:
1 Paediatric patient has severe active Crohn's disease; and
2 Any of the following:
2.1 Patient has a Paediatric Crohn's Disease Activity Index (PCDAI) score of greater than or equal to 30; or
2.2 Patient has extensive small intestine disease; and
3 Patient has tried but had an inadequate response to, or has experienced intolerable side effects from, prior systemic therapy with immunomodulators at maximum tolerated doses (unless contraindicated) and corticosteroids; and
4 Surgery (or further surgery) is considered to be clinically inappropriate.

Renewal – Crohn's disease (adults)
Applications only from a gastroenterologist or Practitioner on the recommendation of a gastroenterologist. Approvals valid for 6 months. All of the following:
1 Either:

Either:
CDAI score has reduced by 100 points from the CDAI score when the patient was initiated on vedolizumab; or
CDAI score is 150 or less; or

Both:
The patient has experienced an adequate response to treatment but the CDAI score cannot be assessed; and
Applicant to indicate the reason the CDAI score cannot be assessed; and
Vedolizumab to administered at a dose no greater than 300 mg every 8 weeks.

Renewal – Crohn's disease (children)
Applications only from a gastroenterologist or Practitioner on the recommendation of a gastroenterologist. Approvals valid for 6 months. All of the following:
1 Either:

Either:
PCDAI score has reduced by 10 points from the PCDAI score when the patient was initiated on vedolizumab; or
PCDAI score is 15 or less; or
Both:
The patient has experienced an adequate response to treatment but the PCDAI score cannot be assessed; and
Applicant to indicate the reason the PCDAI score cannot be assessed; and
Vedolizumab to administered at a dose no greater than 300 mg every 8 weeks.

In making this recommendation, the Committee noted the lack of direct head to head trials comparing vedolizumab to first line TNF-α inhibitor agents such as infliximab and adalimumab and the limited evidence on the efficacy of TNF-α inhibitor agents after prior vedolizumab use in CD, however noted the evidence of treatment benefit of vedolizumab in TNF-α inhibitor treatment naïve patients. The Committee noted and agreed with the Gastrointestinal Subcommittees 2017 recommendation for funding if cost-neutral (same access criteria as infliximab or adalimumab), and if a registered product is available.

8.5. The Committee **recommended** that vedolizumab be listed as a second line biologic treatment for Crohn's disease with a high priority, subject to the following Special Authority criteria:

Initiation – Crohn's disease (adults)
Applications only from a gastroenterologist or Practitioner on the recommendation of a gastroenterologist. Approvals valid for 4 months.

All of the following:
1 Patient has severe active Crohn's disease; and
2 Any of the following:
2.1 Patient has a Crohn's Disease Activity Index (CDAI) score of greater than or equal to 300; or
2.2 Patient has extensive small intestine disease affecting more than 50 cm of the small intestine; or
2.3 Patient has evidence of short gut syndrome or would be at risk of short gut syndrome with further bowel resection; or
2.4 Patient has an ileostomy or colostomy, and has intestinal inflammation; and
3 Patient has tried but had an inadequate response to, or has experienced intolerable side effects from, prior treatment with infliximab and/or adalimumab therapy; and
4 Surgery (or further surgery) is considered to be clinically inappropriate.

Initiation – Crohn's disease (children)
Applications only from a gastroenterologist or Practitioner on the recommendation of a gastroenterologist. Approvals valid for 4 months.

All of the following:
1 Child has severe active Crohn's disease; and
2 Any of the following:
2.1 Patient has a Paediatric Crohn's Disease Activity Index (PCDAI) score of greater than or equal to 30; or
2.2 Patient has extensive small intestine disease; and
3 Patient has tried but had an inadequate response to, or has experienced intolerable side effects from, prior treatment with infliximab and/or adalimumab therapy; and
4 Surgery (or further surgery) is considered to be clinically inappropriate.

Renewal – Crohn's disease (adults)
Applications only from a gastroenterologist or Practitioner on the recommendation of a gastroenterologist. Approvals valid for 6 months. All of the following:
1 Either:
- 1.1 Either:
- 1.1.1 CDAI score has reduced by 100 points from the CDAI score when the patient was initiated on vedolizumab; or
- 1.1.2 CDAI score is 150 or less; or
- 1.2 Both:
- 1.2.1 The patient has experienced an adequate response to treatment but the CDAI score cannot be assessed; and
- 1.2.2 Applicant to indicate the reason the CDAI score cannot be assessed; and
- Vedolizumab to administered at a dose no greater than 300 mg every 8 weeks.

Renewal – Crohn's disease (children)
Applications only from a gastroenterologist or Practitioner on the recommendation of a gastroenterologist. Approvals valid for 6 months. All of the following:
1 Either:
- 1.1 Either:
- 1.1.1 PCDAI score has reduced by 10 points from the PCDAI score when the patient was initiated on vedolizumab; or
- 1.1.2 PCDAI score is 15 or less; or
- 1.2 Both:
- 1.2.1 The patient has experienced an adequate response to treatment but the PCDAI score cannot be assessed; and
- 1.2.1 Applicant to indicate the reason the PCDAI score cannot be assessed; and
- Vedolizumab to administered at a dose no greater than 300 mg every 8 weeks.

In making this recommendation, the Committee noted the high health need of both adults and children with severe Crohn's disease who have received an inadequate response or experienced intolerable side-effects to infliximab or adalimumab, the evidence of efficacy with vedolizumab in this setting, the favourable side effect profile, suitability and the comparative cost of alternative treatments to vedolizumab. The Committee noted and agreed with the Gastrointestinal Subcommittee's 2017 recommendation to fund vedolizumab for Crohn's disease with a high priority.

8.6. The Committee **recommended** that vedolizumab be listed as a first line biologic treatment for moderately to severely active ulcerative colitis with a medium priority, subject to the following Special Authority criteria:

Initiation – Ulcerative colitis
Applications only from a gastroenterologist or Practitioner on the recommendation of a gastroenterologist.
Approvals valid for 4 months.
All of the following:
Patient has histologically confirmed ulcerative colitis; and
Either:
Patient has a total score of 6 to 12 on the Mayo scale and an endoscopic subscore of 2 or 3; or
Patient has a score of at least 65 on the Paediatric Ulcerative Colitis Activity Index (PUCAI); and
Patient has tried but had an inadequate response to, or has experienced intolerable side effects from, prior systemic therapy with immunomodulators at maximum tolerated doses for an adequate duration (unless contraindicated) and corticosteroids; and
Surgery (or further surgery) is considered clinically inappropriate.

Renewal – Ulcerative colitis
Applications only from a gastroenterologist or Practitioner on the recommendation of a gastroenterologist.
Approvals valid for 6 months.
All of the following:
Patient has experienced, or maintained a response (see Note) and the benefit of continuing treatment with vedolizumab outweighs the risks; and
Vedolizumab will be used at a dose no greater than 300 mg intravenously every 8 weeks.
Note: Response is defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding sub score of ≥1 or a rectal bleeding subscore of 0 or 1.

8.7. In making this recommendation, the Committee noted that the 2017 Gastrointestinal Subcommittee recommendation for vedolizumab to be funded in a first line setting if cost-neutral to infliximab, and if a registered product is available. The Committee noted that new evidence demonstrates a clinically significant and durable response with vedolizumab in ulcerative colitis for TNF-α inhibitor naïve patients, although noted that evidence from clinical trials regarding the impact of vedolizumab on surgical intervention was minimal because this intervention is less common in ulcerative colitis than in Crohn's disease; the Committee considered that based on this evidence, it recommended listing with a medium priority.

8.8. The Committee **recommended** that vedolizumab be listed as a second line biologic treatment of moderately to severely active ulcerative colitis with a high priority, subject to the following Special Authority criteria:

Initiation – Ulcerative colitis
Applications only from a gastroenterologist or Practitioner on the recommendation of a gastroenterologist.
Approvals valid for 4 months.
All of the following:
Patient has histologically confirmed ulcerative colitis; and
Either:
Patient has a total score of 6 to 12 on the Mayo scale and an endoscopic subscore of 2 or 3; or
Patient has a score of at least 65 on the Paediatric Ulcerative Colitis Activity Index (PUCAI); and
Patient has tried but had an inadequate response to, or has experienced intolerable side effects from, prior treatment with infliximab and/or adalimumab therapy; and
Surgery (or further surgery) is considered clinically inappropriate.

Renewal – Ulcerative colitis
Applications only from a gastroenterologist or Practitioner on the recommendation of a gastroenterologist.
Approvals valid for 6 months.
All of the following:
Patient has experienced, or maintained a response (see Note) and the benefit of continuing treatment with vedolizumab outweighs the risks; and
Vedolizumab will be used at a dose no greater than 300 mg intravenously every 8 weeks.
Note: Response is defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding sub score of ≥1 or a rectal bleeding subscore of 0 or 1.

8.9. In making this recommendation, the Committee noted the high health need of both adults and children with moderately to severely active ulcerative colitis who have received an inadequate response to infliximab, or experienced intolerable side effects from infliximab; the evidence of efficacy with vedolizumab in this setting; the favourable side effect profile, suitability and the comparative cost of alternative treatments to vedolizumab. The Committee noted and agreed with the Gastrointestinal Subcommittee's 2017 recommendation to fund vedolizumab for ulcerative colitis with a high priority.

Discussion

8.10. PTAC and PTAC Subcommittees may differ in the advice they provide to PHARMAC, including recommendations' priority, due to the committees' different, albeit complementary, roles, expertise, experience, and perspectives.

Vedolizumab

8.11. The Committee noted that vedolizumab is a humanised monoclonal antibody which selectively binds to the α4β7 integrin on T-lymphocytes that are present in the gastrointestinal tract and cause characteristic inflammation in Crohn's disease and ulcerative colitis. The Committee noted vedolizumabs binds selectively to the integrin unique to the bowel, resulting in a gut-specific mechanism of action. The Committee considered that this gut specificity may be associated with a reduction in systemic side effects, however, may similarly result in a limited effect of vedolizumab on the prevention and management of extraintestinal manifestations associated with Crohn's disease and ulcerative colitis.

8.12. The Committee noted that vedolizumab is proposed to be used for patients with moderately to severely active ulcerative colitis or severe Crohn's disease who have experienced either inadequate response, intolerable side effects, or loss of response with the currently available TNF-α inhibitors The Committee noted vedolizumab induction therapy is typically given as 300 mg initially and at week two, with maintenance dosing of 300 mg at week six, then every eight weeks. The Committee considered that an additional 300 mg dose at week 10 may be considered in patients who received suboptimal response after induction therapy. The Committee noted that all doses (induction and maintenance) are administered via IV infusion over a period of approximately 30 minutes in a hospital setting.

8.13. The Committee noted that, in March 2017, the Gastrointestinal Subcommittee considered the clinician application for vedolizumab for the treatment of patients with Crohn's disease and ulcerative colitis who have either had failure of, become refractory to, or experienced severe and intractable side effects from TNF-α inhibitor treatment(s) and:

8.13.1. Recommended that vedolizumab be funded for Crohn's disease, in a first line setting if cost neutral with infliximab and adalimumab if a registered product becomes available; and

8.13.2. Recommended that vedolizumab be funded for Crohn's disease, in a second line setting with a high priority for primary non-responders to infliximab, if a registered product becomes available; and

8.13.3. Recommended that vedolizumab be funded for ulcerative colitis, in a first line setting if cost neutral with infliximab if a registered product becomes available; and

8.13.4. Recommended that vedolizumab be funded for ulcerative colitis, in a second line setting with a high priority for primary and secondary non-responders to infliximab, if a registered product becomes available.

8.14. The Committee noted that, in November 2017, PTAC noted that vedolizumab was neither registered nor sought for registration in New Zealand, and noted that PHARMAC intended to invite Takeda (the supplier of vedolizumab) to submit an application for funding. At that time, PTAC requested it review the evidence from the supplier when applications were made for funding and registration in New Zealand.

8.15. The Committee noted that, in February 2019, PTAC noted that PHARMAC had undertaken an economic analysis for vedolizumab and the proposal had been ranked against other proposals. At that time, PTAC recommended that it be presented a full paper

on vedolizumab, and that it could reconsider its advice on vedolizumab, following that paper.

Health need

8.16. The Committee noted that the current treatment paradigm for management of inflammatory bowel disease (IBD) i.e. patients with Crohn's disease and ulcerative colitis, typically begins with aminosalicylates and escalates to steroid treatment if patients experience flare-ups and disease progression. The Committee noted that, following failure of steroid treatment to manage symptoms, patients may be initiated on immunomodulators such as azathioprine, or TNF-α inhibitor treatment for patients who have not responded to corticosteroids and/or immunosuppressive agents, or have experienced an adverse event or become unable to tolerate corticosteroids and/or immunosuppressive agents. The Committee noted that calcineurin inhibitors are not a feature of New Zealand clinical practice in the treatment of IBD but are used internationally. The Committee noted that for patients for whom biologic therapy does not elicit a response, surgical resection is an option, with more favourable long-term outcomes typically seen in ulcerative colitis patients.

8.17. The Committee considered that more data is needed on whether early aggressive therapy is more beneficial than a step-up treatment approach in the longer term for the treatment of inflammatory bowel diseases, particularly with regard to whether early aggressive therapy has a role in altering the natural history of the disease.

8.18. The Committee noted that the majority of Crohn's disease patients are treated with adalimumab as their first biologic agent, with infliximab used first line in approximately 10-15% of cases. The Committee considered that infliximab is the most common initial biologic agent for patients presenting to hospital with acute Crohn's disease such as those presenting with fistulising disease. The Committee noted that approximately half of Crohn's disease patients who experience primary non-response to a TNF-α inhibitor are likely to experience the same with a second TNF-α inhibitor, and 23% to 46% of those with prior TNF-α inhibitor treatment failure are likely to experience treatment failure (secondary loss of response) to a second TNF-α inhibitor at 12 months (Ben-Horin et al. Autoimmun Rev. 2014;13:24-30).

8.19. The Committee noted that the health need for the IBD patient population is high. Members noted that children and adolescents presenting with IBD are more likely to be diagnosed with severe disease but are less likely to have the complications seen in adult patients such as fistulae, abscesses, and strictures that are associated with longer duration disease (Jakobsen et al. Aliment Pharmacol Ther. 2011;34:1217-24; Duricova et al. J Crohns Colitis. 2014;8:1351-61). Children with ulcerative colitis have more extensive disease after presentation, a higher risk of being treated with systemic steroids and azathioprine⁄ mercaptopurine, a higher frequency of steroid dependency and a more severe disease course.

8.20. Members noted that a non-experimental study investigating the health care utilisation and cost for ulcerative colitis in Australia (Gibson et al. J Crohns Colitis. 2014;8:598-606). The Committee noted that the mean (SD) 3-month UC-related health care cost per patient was reported as AUD $2914 ($3447); with mean for patients in remission, $1970; mild disease, $3736; and moderate/severe disease, $4162; and that patients in remission had the least work and activity impairment. Additionally, the Committee noted that ulcerative colitis patients have a lower health related quality of life than the general population, and that the most important treatment attribute was efficacy, but that patients also value avoiding steroids, and prefer a fast onset of effect (Hagelund et al. Curr Med Res Opin. 2020;36:771-779). The Committee considered that the health system costs, and quality of life impacts would be similar for Crohn's disease.

8.21. Evidence for vedolizumab in Crohn's disease

8.22. The Committee noted the results of the double-blind, placebo-controlled GEMINI II induction and maintenance trials of 829 patients with Crohn's disease; in the induction trial, patients received either intravenous vedolizumab 300 mg (N=220) or placebo (N=148) at weeks 0 and 2, and 747 patients received open-label vedolizumab at weeks 0 and 2. The Committee noted that in the maintenance phase, patients received 300 mg vedolizumab 4-weekly (N=154), 8-weekly (N=154) or placebo (N=153) (Sandborn et al. N Engl J Med 2013; 369:711-21).

- The Committee noted that, in the induction phase, 31.4% of the patients receiving vedolizumab achieved a clinical response, compared with 25.7% in the placebo treatment arm at week 6 (p=0.23). The Committee also noted that, 14.5% of the vedolizumab group and 6.8% of the placebo group achieved clinical remission at week 6 (P=0.02). Of the patients receiving open label vedolizumab, 17.7% achieved clinical remission and 34.4% had a clinical response at week 6.
- The Committee noted that, in the induction phase, 39.0% of patients receiving vedolizumab every 8 weeks and 36.4% receiving vedolizumab every 4 weeks achieved clinical remission, compared with 21.6% of patients receiving placebo at week 52 (P<0.001 and P=0.004 for the comparison of the two vedolizumab groups, respectively, with placebo). The Committee noted that patients were not stratified by previous TNF-α inhibitor exposure
- The Committee noted that the results from GEMINI II were similar to those seen in a 2018 meta-analysis where the rates of corticosteroid-free remission was 25% at week 14 (95%, CI 20% to 31%) and 31% at month 12 (95%, CI 20% to 45%) (Schreiber et al. J Gastroenterol. 2018;53:1048-1064).

8.23. The Committee noted the results of the double-blind, placebo-controlled GEMINI III trial of 416 patients with Crohn's disease in whom previous therapy with a TNF-α inhibitor had failed were given 300 mg of vedolizumab (N=209) or placebo (N=207) intravenously at weeks 0, 2, and 6 (Sands et al. Gastroenterology 2014; 147(3): 618-27). The Committee noted that, at week 6, among patients with prior TNF-α inhibitor failure, 15.2% achieved clinical remission in the vedolizumab group compared with 12.1% in the placebo group (P=0.433). The Committee noted that a clinical response was achieved in 39.2% of vedolizumab patients compared with 22.3% of the placebo patients (P=0.001).

8.24. The Committee noted that, among patients naïve to TNF-α inhibitor treatment, remission occurred in 31.4% of the vedolizumab group compared with 12.0% in the placebo group. The Committee also noted that clinical response was achieved in 39.2% of the vedolizumab group compared with 24.0% of the placebo group.

8.25. The Committee noted that, at week ten, among patients with prior TNF-α inhibitor failure, 26.6% achieved clinical remission in the vedolizumab group compared with 12.1% in the placebo group (P=0.001). The Committee noted that a clinical response was achieved in 46.8% of vedolizumab patients compared with 24.8% of the placebo patients (P=0.001). The Committee also noted that among patients naïve to TNF-α inhibitors, clinical remission was 35.3% for vedolizumab compared with 16.0% with placebo, and clinical response was 51.0% with vedolizumab compared with 22.0% with placebo.

8.26. The Committee noted the results of a study performed at five hospitals in Paris comparing vedolizumab to ustekinumab in 239 patients with Crohn's disease that have not responded to TNF-α inhibitor therapy (Alric et al. Aliment Pharmacol Therap.2020;51:948-57). The Committee noted that at week 14, the rate of clinical remission was similar between vedolizumab and ustekinumab (46.1% vs 42.3%; OR=0.86, 95% CI 0.49 to 1.50, P=0.59), but that at week 48 ustekinumab was associated with a higher clinical remission rate (54.4% vs 38.3%; OR=1.92, 95% CI 1.09 to 3.39, P = 0.03) and treatment persistence (71.5% vs 49.7%; OR=2.54, 95% CI 1.40 to 4.62], P<0.01) than vedolizumab. The Committee considered that results from both treatments were good results in the context of treatment for Crohn's disease. Members considered that the study used a robust definition for steroid-free remission and that similar results were reported for this outcome.

Evidence for vedolizumab in ulcerative colitis

8.27. The Committee noted the results of the double-blind, placebo-controlled GEMINI I trial of 374 patients with ulcerative colitis who received 6 weeks of induction (randomised 2:1) with vedolizumab 300 mg intravenously (N=225) or placebo (N=149) at days 1 and 15 followed by 46 weeks maintenance (randomised 1:1:1) with either 4-weekly vedolizumab 300 mg (N=125), 8-weekly vedolizumab 300 mg (N=122) or placebo (N=126; Feagan et al. N Engl J Med 2013; 369:699-710)

8.27.1. The Committee noted that the primary outcome of induction was clinical response at week 6 (Mayo score reduction of ≥3 points and decrease of 30% from baseline, with decrease of ≥1 point on rectal bleeding sub-score or absolute sub-score of 0 or 1) which was 47.1% with vedolizumab vs 25.5% with placebo (P<0.001).

8.27.2. The Committee noted that the primary outcome of maintenance treatment was clinical remission at week 52, which was reported in 41.8% with vedolizumab 8-weekly vs 44.8% with vedolizumab 4-weekly vs 15.9% with placebo (P<0.001).

8.27.3. The Committee noted that mucosal healing at week 12 was reported in 52% with vedolizumab 8-weekly vs 56% vedolizumab 4-weekly vs 20% with placebo; members considered that this was clinically relevant but not as crucial a trial endpoint as clinical response and remission.

8.27.4. The Committee noted that a post-hoc analysis of the GEMINI 1 trial reported a greater improvement in health-related quality of life scores with vedolizumab compared with placebo (Feagan et al. Aliment Pharmacol Ther. 2017;45:264-75).

8.28. The Subcommittee noted the results of the VARSITY trial; a phase IIIb, randomised, double-blind, active-controlled superiority trial investigating vedolizumab (300 mg intravenously at weeks 0, 2, 6 and then 8-weekly, plus subcutaneous placebo injections); or adalimumab (160 mg week 0, 80 mg week 3, then 40 mg 2-weekly thereafter, plus placebo intravenous infusions) in 771 adult patients with ulcerative colitis (Sands et al. N Engl J Med 2019; 381: 1215-26). The Committee noted that the VARSITY trial provided a head-to-head comparison of these two agents in ulcerative colitis and noted that this evidence had not been formally reviewed by the Gastrointestinal Subcommittee.

8.28.1. The Committee noted that the primary endpoint was clinical remission at week 52 (≤2 on Mayo score; no sub-score >1) and that 31.3% of patients who received vedolizumab were in remission at week 52 vs 22.5% with adalimumab (P=0.006).

8.28.2. The Committee noted that the trial reported a response in 67.1% of patients who received vedolizumab at 14 weeks and considered that the 6-week assessment of response and remission were too early to appropriately assess this agent. Members considered that there was good durability of clinical response with vedolizumab. The Committee further noted that the response rate with adalimumab was slightly lower than vedolizumab at most time points, but with a similar response after 52 weeks. The Committee noted that a clinical response at week 14 was observed in 67.1% of vedolizumab patients vs 45.9% of adalimumab patients (P<0.05); among patients with prior anti-TNF exposure, clinical response at week 14 was 55.7% with vedolizumab vs 32.1% with adalimumab (P<0.05); and among those naïve to anti-TNFs, response at week 14 was 70.1% with vedolizumab vs 49.5% with adalimumab (P<0.05).

8.28.3. The Committee noted that corticosteroid-free clinical remission (a secondary outcome assessed only in patients receiving corticosteroids at baseline) was reported in 12.6% with vedolizumab vs 21.8% with adalimumab (difference not significant).

8.28.4. Members considered that the results from the VARSITY trial suggest vedolizumab is more effective than adalimumab as a first-line treatment for ulcerative colitis. Members considered that the outcomes demonstrated with vedolizumab were likely as good as, or better than, outcomes seen in clinical practice with infliximab in New Zealand (relative to outcomes with adalimumab) and considered that while adalimumab is likely less effective than infliximab in ulcerative colitis, it is likely that outcomes with vedolizumab as a first-line agent are superior to those with infliximab as a first-line treatment in ulcerative colitis.

8.29. Members noted evidence from the VISIBLE 1 trial of subcutaneous vedolizumab in patients with ulcerative colitis; 54 patients received intravenous vedolizumab, 106 received subcutaneous vedolizumab and 56 received placebo (Sandborn et al. Gastroenterology. 2020;158:562-72.e12). Members considered that the results at 52 weeks were similar to (or slightly better than) those in the GEMINI I trial, with about 40% of patients in clinical remission at 52 weeks in both vedolizumab groups, suggesting that the subcutaneous formulation was equivalent to intravenous vedolizumab. The Committee noted that 72.2%, 64.2% and 28.6% of patients who received IV vedolizumab, subcutaneous vedolizumab and placebo, respectively had durable clinical responses at 52 weeks. Members considered that if this data were extrapolated to use in Crohn's disease, the response rate would be less, although still demonstrated a clinically relevant response.

8.30. The Committee reviewed other evidence of vedolizumab in both Crohn's disease and ulcerative colitis:

8.30.1. The Committee noted the results of a long-term extension study that included patients from the GEMINI II and III studies who had up to 152 weeks of vedolizumab exposure (Vermeire et al. J Crohns Colitis. 2017;11:412-24). The Committee noted that among patients with response at week 6 in GEMINI II who received vedolizumab continuously, 83% (N=100/120) and 89% (N=62/70) of patients were in remission after 104 and 152 weeks, respectively. The Committee noted that increased dosing frequency from every 8 weeks to every 4 weeks improved outcomes in patients who had withdrawn early from GEMINI II, with 47% (N=27/57) experiencing clinical response and 32% (N=18/57) in remission at week 52 of the long term extension (up from 39% and 4% before the dose increase).

8.30.2. The Committee noted the results of a long-term extension study that included patients from the C13004 and GEMINI I studies who had up to 152 weeks of vedolizumab exposure (Loftus Jr et al. J Crohns Colitis. 2017;11: 400-11). The Committee noted that among patients with response at week 6 of GEMINI I, 88% (120/136) and 96% (70/73) were in remission after 104 and 152 weeks respectively. The Committee considered that increased dosing frequency from every 8 weeks to every 4 weeks improved outcomes in patients who had withdrawn early from GEMINI I, with 41% experiencing clinical response and 28% in remission at week 52 of the long term extension (up from 19% and 6% before the dose increase).

8.30.3. The Committee noted that the authors reported analysis excluding those with missing data, and a separate analysis treating all those with missing data as treatment failures. The Committee considered that missing clinical trial data is likely due to a variety of reasons, and that there were a significant number of patients who represented missing data at week 152 as they had not yet reached 152 weeks of vedolizumab exposure during GEMINI LTS. The Committee considered that in this context, it was reasonable to appraise the long-term efficacy of vedolizumab based on the results which excluded those with missing data from the analysis. The Committee considered that the results suggest the rate of loss of response with vedolizumab is less than 10% per year, with similar long-term loss of response between ulcerative colitis and Crohn's disease. The Committee considered that while the proportion of patients with prior anti-TNF failure in remission was lower than the proportion in remission among those without prior

anti-TNF failure, the loss of response rates between the two groups in GEMINI LTS was comparable.

8.30.4. The Committee noted a meta-analysis that included 3216 patients with ulcerative colitis from several “real-world” open-label studies of vedolizumab which reported clinical remission in approximately 40% at 12 months and clinical response in 52% (Schreiber et al. J Gastroenterology. 2018;53:1048). Members considered this demonstrated similar treatment effect to results demonstrated in GEMINI 1 which demonstrated remission rates of 42% at 12 months.

8.30.5. The Committee note that the same meta-analysis included patients with Crohn’s disease and reported slightly lower rates of clinical remission (30%) and clinical response (40%) in these patients at 52 weeks compared with rates of patients with ulcerative colitis, and the Committee considered the clinical response was again similar to that demonstrated in GEMINI II (clinical response 39% at 52 weeks with vedolizumab 8-weekly).

8.30.6. The Committee noted that mucosal healing, a component of the concept of 'deep remission', was reported in the same paper with rates at 12 months varying from 33% to 77% for ulcerative colitis patients, and 6% to 63% for Crohn’s patients. The Committee noted that mucosal healing was highly variable for both diseases and considered that rates of approximately 50% would be clinically relevant, but variability contributed by different definitions of mucosal healing between clinical trials made assessment difficult.

8.30.7. The Committee noted the results of the open-label, multi-centre, “real-world” Cross Pennine study that reported long-term effectiveness and safety with vedolizumab in 135 patients with Crohn’s disease and 68 patients with ulcerative colitis in the UK (Lenti et al. Digestive Liver Dis. 2018;50:1299-1304).

- The Committee noted that this study assessed treatment response from 14 weeks (rather than 6 weeks) which members considered was appropriate for assessment of vedolizumab’s effect. The Committee noted that 96% and 66% of Crohn’s disease and ulcerative colitis patients had prior exposure to a TNF-α inhibitor.
- The Committee noted that at 14 weeks 40% and 42.6% of patients with Crohn’s disease and ulcerative colitis, respectively, achieved a partial response and 38.5% and 48.5%, respectively, achieved remission (Figure 1. Lenti et al. 2018). The Committee noted that at 52 weeks, a total of 63.9% of patients with Crohn’s disease and 82.5% of patients with ulcerative colitis in this study achieved a response or remission.
- The Committee considered that the combined rates of response and remission reported in this study may be an outlier compared with the other evidence for vedolizumab in this setting possibly due to lack of objective measures of disease activity.

8.30.8. The Committee considered that the understanding of vedolizumab in Crohn’s disease and ulcerative colitis had developed over time and that, in retrospect, outcome assessments in some trials were performed too early in the treatment course. Members considered that week 14 (rather than week 6 or week 10) was a more reasonable timepoint for initial assessment of treatment effect in the clinical trials.

8.30.9. Members noted evidence for three-year effectiveness of vedolizumab in a prospective multi-centre, French cohort study of 173 patients with Crohn’s disease and 121 patients with ulcerative colitis, of which the majority (90% and 78%, respectively) had prior exposure to at least two TNF-α inhibitor therapies (Amiot et al. Aliment Pharmacol Ther. 2019;50:40-53).

- Members noted that the remission rate in patients with Crohn's disease was 30.0% at one year, as expected, with loss of remission occurring over time resulting in 19.9% in remission at three years; remission rates at one year and three years in patients with ulcerative colitis were 42.1% and 36.1%, respectively.
- Members noted that the difference between the response rate (47.4%) and remission rate (30.0%) in patients with Crohn's disease at one year was roughly 15%, as expected, and noted that the proportion in response was 21.1% at three years.
- Members noted that 36.1% of patients with ulcerative colitis experienced steroid-free clinical remission at three years and that 62.3% of patients were still in steroid-free clinical remission at week 162.

8.30.10. The Committee noted that the pharmacokinetics of vedolizumab are unconventional, and that the half-life cannot be determined via concentration curves. The Committee noted that the half-life of effect, rather than the half-life of the drug, is needed to determine the correct dose. The Committee noted that the elimination half-life of vedolizumab is approximately 25 days and, based on data from the GEMINI studies, low albumin concentration and high body mass were identified as predictors of accelerated vedolizumab clearance.

8.30.11. The Committee noted that, although there are intravenous and subcutaneous formulation of vedolizumab available, the current application only includes intravenous vedolizumab. The Committee noted that the two formulations would have the same clearance, but the bioavailability could be less with the subcutaneous formulation.

8.30.12. The Committee noted three studies linking lower trough concentrations of vedolizumab with worse therapeutic outcomes for IBD which support fixed dosing of 300 mg, but noted that the evidence did not take into account covariates such as age, gender, serum albumen or obesity:

- Al-Bawardy et al. Inflamm Bowel Dis. 2019;25:580–6
- Dreesen et al. Clin Gastroenterol Hepatol. 2018;16:1937–46
- Pouillon et al. BMC Med. 2019;17:89

8.30.13. The Committee noted that therapeutic drug monitoring (TDM) is a treatment strategy that has a target drug concentration rather than a target dose that determines effect. Members noted that TDM may alter dosing stratagem. Members considered that it is currently unclear whether disease symptoms should drive decisions on drug dosing, or whether use of TDM is better for vedolizumab in IBD. Drug/antibody concentration testing for vedolizumab may be useful in non-responders at the end of induction or in those with confirmed secondary loss of response, but they are currently not sufficient to guide specific individual treatments (Papamichael et al. Clin Gastroenterol Hepatol. 2019;17:1655-68).

8.30.14. The Committee noted that there are emerging data indicating that target trough concentrations for vedolizumab should be around 25 ug/mL for initial clinical response for ulcerative colitis patients (Takatsu et al. Core Evid. 2020;15:7-20) and that the target concentration may differ between induction and maintenance therapy. The Committee noted that vedolizumab is selective to the gut and considered that increasing the dose may not lead to an increase in treatment related adverse events as seen with some TNF-α inhibitor treatment.

8.30.15. The Committee noted a study investigating the safety of vedolizumab for ulcerative colitis and Crohn's disease showing that, in the GEMINI 1 and 2 studies, 4% of patients developed antibodies against vedolizumab, which may contribute to a reduced response (Colombel et al. Gut. 2017;66:839-851). The Committee considered the level of anti-drug antibodies appeared to be low compared to

treatment with TNF-α inhibitors and also noted that the addition of an immunomodulator to vedolizumab treatment neither enhances drug levels nor improves therapeutic response (Ungar et al. Clin Gastroenterol Hepatol. 2018;16:697-705.e7) indicating an advantage of patients not requiring concomitant immunomodulator therapy which are commonly used with TNF-α inhibitors.

8.30.16. The Committee noted that the evidence for vedolizumab included individual randomised controlled clinical trials and cohort and observational studies that include patients with ulcerative colitis and patients with Crohn's disease. The Committee considered that this combined evidence was due to the many similarities between these diseases and the overlap in treatment approaches with biologics in particular. The Committee considered that differences relating to surgery were the key differences in the evidence for these diseases.

8.30.17. The Committee noted that to date there are no unknown adverse reactions of concern over alternate funded biologics, and that demyelinating disorders are less common than with other monoclonal antibodies because vedolizumab is specific to the gut. The Committee noted that treatment with vedolizumab did not differ in rates of serious infections, haematologic or serum chemical profiles, or liver-function test results when compared to placebo.

8.30.18. The Committee noted that treatment with vedolizumab did not appear to increase the risk of postoperative infection or complications in patients with ulcerative colitis undergoing abdominal surgery, and had fewer complications than similar patients who received TNF-α inhibitor therapy prior to surgery (Law et al. J Crohns Colitis. 2018;12:538-545, Yung et al. Inflamm Bowel Dis. 2018;24:2327-2338). The Committee noted, however, that treatment with vedolizumab was associated with an increase in postoperative infectious complications in patients with Crohn's disease, but that these results were possibly compromised by concomitant use of corticosteroids, which are associated with an increased risk of postoperative complications (Lightner et al. Curr Drug Targets. 2019;20:1317-22).

8.30.19. The Committee noted the evidence of efficacy and safety of vedolizumab in paediatric patients, children and young adults with Crohn's disease or ulcerative colitis (Conrad et al. Inflamm Bowel Dis 2016;22:2425-31; Ledder et al. J Crohn's Colitis 2017;11:1230-7; Schneider et al. BMC Gastroenterol. 2018;18:140; Singh et al. Inflamm Bowel Dis 2016;22:2121-6). The Committee considered that the efficacy and safety reported in these studies suggests that vedolizumab may be similarly effective in children and adults, but was limited by these being small, non-experimental studies and the age ranges were not necessarily applicable to New Zealand. The Committee noted that vedolizumab is not Medsafe-approved for use in children. The Committee considered that there are risks associated with exposure to immunosuppressant therapies that may be used in combination for children e.g. risk of lymphoma if already treated with thiopurines; which could make vedolizumab treatment preferrable as concomitant immunosuppressant use isn't necessary for vedolizumab.

8.30.20. The Committee noted the evidence provided by the applicants regarding the treatment failure rate of TNF-α inhibitor therapy in ulcerative colitis or Crohn's disease and several other relevant references. The Committee also noted the following additional evidence regarding vedolizumab, Crohn's disease and ulcerative colitis:

- Feagen et al. J Crohns Colitis. 2019;13:50-7
- Kopylov et al. Dig Liver Dis. 2019;51:68-74
- Loftus et al. J Crohns Colitis. 2017;11:400-11
- Loftus et al. Clin Exp Gastroenterol. 2020;13:211-20
- Motoya et al. PLoS One. 2019;14:e021298

- Osterman et al. Aliment Pharmacol Ther. 2019;49:408-18
- Rosario et al. (J Crohns Colitis. 2017;11:921-9
- Sandborn et al. J Crohns Colitis. 2019;13:172-81
- Varvarynets et al. Wiad Lek. 2018;71:346-9) [Article in Ukrainian]
- Yajnik et al. Adv Ther. 2017;34:542-59

8.30.21. The Committee considered that the evidence for vedolizumab for ulcerative colitis and Crohn's disease from prospective cohort studies was of moderate to good quality, supported by "real world" observational data, and considered that this evidence was applicable to patients in New Zealand. However, the Committee considered this evidence did not inform a definite duration of treatment with vedolizumab or appropriate stopping criteria, nor did it provide evidence of hospitalisation rates for severe disease or evidence of colectomy prevention in either ulcerative colitis or Crohn's disease.

8.30.22. The Committee considered that, if vedolizumab were to be funded for IBD, that some patients would be in corticosteroid-free remission at one year and that this was an important goal for patients and clinicians.

Suitability

8.31. The Committee noted that the infusion duration for intravenous administration of vedolizumab is shorter than that of infliximab, and that vedolizumab does not require treatment in combination with immunosuppressants e.g. thiopurines.

8.32. The Committee noted that some wastage could be expected with vedolizumab e.g. due to lower doses for children) The Committee considered that if effective, treatment with vedolizumab would likely be long-term due to its long duration of effect. The Committee considered that the loss of response with vedolizumab is less than 10% per year, and this is likely lower than the 13-15% loss of response per year observed with TNF-α inhibitors.

8.33. The Committee considered that if a subcutaneous vedolizumab formulation were available, it would enable administration in the community and self-administration, however, it may require more frequent administration than the intravenous formulation.

Uptake of vedolizumab in Crohn's disease

8.34. The Committee considered that approximately 46% of patients with Crohn's have disease that is refractory to TNF-α inhibitor therapy. The Committee considered that there is likely to be a small prevalent pool of patients initiating vedolizumab shortly after listing, and this prevalent pool is likely to be larger in Crohn's disease than in ulcerative colitis. The Committee considered that the estimated uptake and number of patients (who may be eligible for vedolizumab as a second-line treatment for severe Crohn's disease) of approximately 280 equivalent full-year patients in year 1, rising to 420 in three years was reasonable. The Committee considered that the rate of failure of maintenance therapy with vedolizumab was likely to be less than that of infliximab.

8.35. The Committee considered there was some uncertainty around how many patients would use vedolizumab after the failure of one TNF-α inhibitor (instead of a second anti-TNF), and considered it is possible that up to 50% could use vedolizumab as an alternative to a second TNF-α inhibitor. The Committee considered it was quite common to exhaust funded treatments within the same class before shifting out of class to a biologic with an alternative mechanism of action and considered that vedolizumab is commonly used overseas after the failure of two prior TNF-α inhibitors.

8.36. The Committee considered that there should be no age restriction in the funding criteria for vedolizumab for Crohn's disease.

Uptake of vedolizumab in ulcerative colitis

8.37. The Committee noted that there was evidence to suggest that vedolizumab is as effective as TNF-α inhibitor therapy and would be appropriate to be used as a first-line biologic after immunomodulators and calcineurin inhibitors, instead of TNF-α inhibitor therapy, in patients with severe ulcerative colitis.

8.38. The Committee considered that 55-60% of UC patients are likely to experience loss of response to infliximab over time. The Committee considered that the estimated uptake and number of patients (who may be eligible for vedolizumab as second-line treatment for moderately to severely active ulcerative colitis) of approximately 75 equivalent full-year patients at year one, increasing to 150 in three years was reasonable, and was consistent with previous considerations of likely patient numbers for second-line treatment of ulcerative colitis.

8.39. The Committee considered it reasonable for children with ulcerative colitis to be eligible for treatment with vedolizumab, noting that there is evidence of efficacy in children aged six to 17 years and noting the health need of children and adolescents with ulcerative colitis.

General

8.40. The Committee noted that since the introduction of TNF-α inhibitors, the need for and rates of surgery for ulcerative colitis and Crohn's disease patients has decreased substantially. The Committee also noted that the pivotal trials for vedolizumab did not show a reduction in surgery rates compared with placebo, and thus considered that longer term follow-up may be required to determine the impact of vedolizumab treatment (and/or other biological treatments) on surgical rates. The Committee considered that the greatest benefit from funding vedolizumab would be increased symptom control and improvement in quality of life measures, and that an appropriate comparator for vedolizumab is adalimumab and/or infliximab.

8.41. The Committee noted that information on the duration of treatment, stopping points for treatment, use of endoscopy, and use of combination therapy was missing from the clinical trial data and commentary submitted by the applicant.

8.42. The Committee suggested that the Gastrointestinal Subcommittee review the application for vedolizumab for the treatment of moderately to severely active ulcerative colitis and provide expert advice on the VARSITY trial evidence (not yet reviewed by the Subcommittee), and the use of therapeutic drug monitoring in this setting.

9. Biologics for inflammatory bowel disease – review of health economic analysis

9.1. The Committee considered that there were a number of biologics previously considered for funding, and in development for use in patients with severe inflammatory bowel disease (IBD). The Committee noted that advice was sought by PHARMAC staff regarding assumptions used in the modelling of cost-effectiveness of treatments for severe IBD.

9.2. The Committee noted that the inclusion criteria in key clinical trials for biologics in ulcerative colitis (UC) and Crohn's disease required patients to have moderate to severely active disease at baseline. The Committee considered that, based on inclusion criteria, fewer than one third of patients with moderate to severe disease are suitable for clinical trials, and those patients with more severe disease are less likely to be represented in clinical trials. The Committee considered that, based on the existing Special Authority criteria, the patients likely to receive biologic treatment in New Zealand have more severe disease than patients enrolled in the key clinical trials. The Committee considered that, as a result, the health-related quality of life (HR-QoL) of patients of eligible patients in New Zealand clinical practice was likely to be poorer than that of patients enrolled in the key clinical trials.

9.3. The Committee noted a systematic review and meta-analysis of health utility of patients with Crohn's disease and UC (Malinowski & Kawalec. Expert Rev Health Econ 2016;16:441-53). The Committee noted the results of the meta-analysis were at times internally inconsistent, with the meta-analysis for UC reporting a lower aggregate utility value i.e. greater loss of quality of life; for moderate disease than for severe disease. The Committee considered there was significant heterogeneity in studies included in the meta-analysis, and many differences in health utilities were based on different methodologies used to collect health utilities, as well as different definitions used to define severe disease; and there may have been differences in the mix of studies providing health utilities at each disease stage, adding further bias and inconsistency.

9.4. The Committee noted the health utilities for UC patients reported in a study of Danish patients (Hagelund et al. Curr Med Res Opin 2020;36:771-9). The Committee noted the health-related quality of life of patients experiencing a self-reported flare was worse for patients with severe disease, compared with those with mild or moderate disease (EQ-5D utility for remission and flare in severe disease 0.82 and 0.45; in moderate disease, 0.81 and 0.53; in mild disease, 0.86 and 0.65 respectively). The Committee noted that the health-related quality of life of patients with a self-reported flare was also worse than the baseline quality of life scores reported in clinical trials of vedolizumab (GEMINI), tofacitinib (OCTAVE) and ustekinumab (UNIFI) for moderate to severe UC. The Committee considered that clinical trials do not necessarily accurately convey the health-related quality of life of those with severe disease, and considered that the difference between utility estimates in reported studies and clinical trials may be affected by differing methods of generating health utilities and differing definitions of disease states.

9.5. The Committee noted a study assessing utility values for patients in corticosteroid-refractory UC, reporting HR-QoL values of 0.79 for remission and 0.32 for "active" UC (Arseneau et al. Clin Gastroenterol Hepatol 2006;4:1135-42). The Committee noted the utility values reported in a UK study of UC patients, (Woehl et al. Gut 2008;57), reported utility values of 0.87 for remission and 0.41 for active UC. The Committee noted that, for the purpose of cost-utility analysis, an important driver of results was the difference between remission and severe disease states, and noted this difference in the Arseneau et al. and Woehl et al. studies was 0.47 and 0.46 respectively. The Committee considered that health-related quality of life gains of this magnitude are generally rare. The Committee considered that there was no available evidence reporting utility gains of this magnitude with ongoing biologic treatment, and members considered that the use of these values in cost-utility analysis may overstate the potential gains from treatment.

9.6. The Committee noted that IBD is associated with increased mortality compared with the rest of the population. The Committee noted that IBD patients are more likely to be diagnosed with cancer (most commonly colorectal cancer or cholangiocarcinoma), and that immunosuppression and complications resulting from surgery are also associated with an increased risk of mortality for IBD patients. The Committee considered that there is a lack of evidence to demonstrate that successful biologic treatment reduces the risk of mortality.

9.7. The Committee noted that NICE guidance recommends that patients should be assessed after 12 months of biologic treatment, and that treatment withdrawal should be considered if suitable. The Committee noted that there were no prospective trials assessing the outcomes of a 12-month stopping rule, and considered that available evidence suggests treatment is rarely stopped after 12 months in clinical practice if a patient is benefitting from treatment.

9.8. The Committee noted a Cochrane review of assessments supporting withdrawal of immunosuppressant or biologic therapy in Crohn's disease, and noted there were no identified prospective trials of withdrawal for biologics (Boyapati RK et al. Cochrane Database Syst Rev 2018;5:CD012540).

9.9. The Committee noted that 'deep remission' is the clinical criterion normally applied to decide if withdrawal of biologic treatment is appropriate. The Committee considered that withdrawal of treatment is rare in clinical practice, and particularly rare in Crohn's disease, due to the high risk of relapse. The Committee considered that even patients whose treatment is withdrawn after achieving deep remission may be at risk of disease relapse.

9.10. The Committee noted a UK systematic review and observational study of relapse following withdrawal from anti-TNF treatment in IBD, which reported relapse rates at 12 and 24 months after stopping of 36% and 54% respectively for Crohn's disease, and 42% and 47% respectively for UC (Kennedy et al. Aliment Pharmacol Ther 2016; 43: 910-23). The Committee noted in the associated non-experimental study that the median duration on anti-TNFs prior to stopping was 29 months for Crohn's disease, and 21 months for UC/IBD unclassified.

9.11. The Committee noted a study of persistence on biologics among Crohn's disease patients in New Zealand and Australia, which reported losses of response of approximately 25% after 1 year and 40% after 2 years (Doecke et al. Aliment Pharmacol Ther 2017;45:542-52). The Committee also noted a New Zealand-based study of Crohn's disease patients receiving adalimumab, which reported 75% continuing adalimumab after 30 months (Thomas et al. N Z Med J 2014;127:1396). The Committee considered that, based on the persistence on biologics in the New Zealand, Australian and UK studies noted above, approximately 60-75% of patients may remain on anti-TNF treatment beyond two years.

9.12. The Committee considered that discontinuation of immunosuppressants and extension of dosing intervals would likely be considered before discontinuation of any biologic treatment. However, the Committee considered that, while reducing the interval between doses to recapture response is common in clinical practice, extension of the dosing interval while achieving a response is generally rare.

9.13. The Committee considered that approximately 10% of patients with UC who experience insufficient disease control with biologic therapy continue despite limited benefit. The Committee considered that the proportion of patients who remain on treatment despite not experiencing optimal disease control was likely larger for Crohn's disease, due to the severity of the disease and the risks of relapse and short-gut syndrome associated with repeated surgical resection. The Committee considered that it was unclear exactly how many Crohn's disease patients remain on treatment despite waning efficacy, and how long patients remain on treatment with limited benefit; however the Committee considered it would be unlikely for the proportion of these patients to exceed 40%.

9.14. The Committee noted that PHARMAC's Prescription for Pharmacoeconomic Analysis (PFPA) recommends hospital inpatient and outpatient costs are calculated using Diagnosis Related Group (DRG) prices, which rely on Weighted Inlier Equivalent Separations New Zealand (WIESNZ) cost weights. The Committee considered that DRG prices often fail to reflect real resource costs to DHBs. The Committee considered that patient-level data from sentinel DHBs would be a more accurate reflection of costs.

9.15. The Committee noted the COIN study from the Netherlands (van der Valk et al. Gut 2014;63:72-9), which reported 3-monthly healthcare costs associated with IBD in a survey of patients. The Committee noted this study reported that medication costs comprised 71% of the total healthcare costs in the Crohn's disease cohort, and 59% of costs in the UC cohort; hospitalisation and surgery respectively comprised 19% and 1% of Crohn's disease costs, and 23% and 1% of UC costs. The Committee considered it was likely that hospitalisations are not the main drivers of healthcare costs in IBD, and surgery is likely to make up a small fraction of IBD costs.

9.16. The Committee considered that not all patients who experience treatment failure proceed to surgery, and that there are some patients who may require surgery despite benefitting from treatment. The Committee considered that many Crohn's disease patients

who require surgery despite benefitting from treatment would be able to return to biologic treatment after surgery and maintain treatment response .

9.17. The Committee considered that it was unclear what proportion of surgeries would feasibly be delayed due to ongoing biologic therapy; however, the Committee noted that few operations would be postponed in patients with severe pancolitis or cancer.

9.18. The Committee noted a systematic review and meta-analysis on the impact of immunosuppressants and biologics on surgeries and hospitalisations in IBD (Mao et al. Aliment Pharmacol Ther 2017;45:3-13). The Committee noted that the meta-analysis reported no reduction in the likelihood of Crohn's disease surgery with vedolizumab (OR 0.43, 95% CI 0.13-1.40). The Committee also noted surgery rates in the UNIFI trial for ustekinumab in UC (Sands et al. N Engl J Med 2019;381:1201-14), which reported no significant difference between the ustekinumab and placebo groups (0.6% vs 1.7%, p=0.34). The Committee considered that while these trials had limited follow-up that and longer-term studies may potentially reveal a higher cumulative reduction in surgery, the currently available evidence suggests that improvement in quality of life, rather than reduction in surgery, is the most relevant treatment outcome that should be assessed.

9.19. The Committee noted the New Zealand Society of Gastroenterology guidelines for the management of refractory UC (Eliadou et al. N Z Med J 2015;128:63-76), which stated that 30% of patients with UC will eventually undergo proctocolectomy; however, the Committee considered the origins of this figure were unclear.

9.20. The Committee noted that the incidence of surgery associated with Crohn's disease have decreased significantly over time, noting that over a 9-year period, the rate of surgery in Alberta Canada decreased from 4.4 per 100 patient years to 3.5 per 100 patient-years, with a shift from emergency to elective surgery (Ma et al. Am J Gastroenterol 2017;112:1840-8).

9.21. The Committee noted a systematic review and meta-analysis of surgery rates for UC, reporting 10-year rates of colectomy of 6.4% (Fumery et al. Clin Gastroenterol Hepatol 2018;16:343-56). The Committee noted evidence from a recent cohort study reporting a rate of colectomy of 0.5% per year (Parragi et al. J Crohn's Colitis 2018 811-8).

9.22. The Committee noted a systematic review of repeat surgery rates in Crohn's disease, reporting a risk of repeat surgery 5 years after initial resection of 25%, and a 10-year risk of 35% (Frolkis et al. Am J Gastroenterol 2014;109:1739-48). The Committee considered that repeat surgery increases the risk of short gut syndrome and the cumulative risk of complications, and as a result, clinicians are generally conservative with regard to progressing patients for surgery.

9.23. The Committee considered that the surgical procedures performed for Crohn's disease are generally different than those performed for UC. The Committee considered that ileal pouch anal anastomosis (IPAA) is a common procedure for UC but is very rarely performed in Crohn's disease, where the more common surgical procedure for Crohn's disease is ileostomy.

9.24. The Committee noted that surgery for UC is generally a one-off cost as the area of inflamed bowel is removed, resolving the symptoms of disease. The Committee considered that fewer than 10% of patients with UC require ongoing stoma care after surgery. The Committee noted that UC surgery is associated with a wide spectrum of morbidity, and considered that avoiding surgery is strongly preferred by patients.

9.25. The Committee noted that international guidelines recommend the use of anti-TNFs after surgical resection in patients considered at risk of post-operative recurrence (Adamina et al. J Crohn's Colitis 2020;155-68; Nguyen et al. Gastroenterol 2017;152:271-5). The Committee considered anti-TNFs appear to be effective in preventing clinical and endoscopic recurrence after surgical resection, and considered that the number of patients

who are treated post-operatively with anti-TNFs was approximately 30%, with this likely to rise up to 50% over time.

9.26. The Committee noted that corticosteroid use was associated with an increased risk of complications after surgery, and considered that the reduction in corticosteroid use over time has likely resulted in a reduction in surgical complications. The Committee considered that while complications following surgical intervention are different after surgeries in patients with Crohn's disease compared with surgery for patients with UC, the rate of complications is unlikely to be significantly different.

10. Quinacrine for the treatment of systemic lupus erythematosus (SLE)

Application

10.1. The Committee reviewed an application for quinacrine in the treatment of systemic lupus erythematosus (SLE).

10.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

10.3. The Committee **recommended** that quinacrine in the treatment of systemic lupus erythematosus (SLE) be declined.

10.4. The Committee made this recommendation based on there being no discernible unmet health need for these patients, no Medsafe registration, that it was difficult for the Committee to evaluate the safety data for the agent, and low-quality evidence of efficacy.

Discussion

10.5. The Committee noted that systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unknown cause and varied severity that can affect virtually any organ of the body. The Committee noted that epidemiological data on SLE occurrence in New Zealand is limited, but that the rate is estimated at 11 people per 100,000, and patients are predominantly female.

10.6. The Committee noted that Māori and Pacific people have a greater relative risk of all types of cutaneous SLE than New Zealand Europeans (relative risk: 2.47; 95% CI 1.67 to 3.67), particularly discoid lupus (relative risk: 5.96; 95% CI 3.06 to 11.6) (Jarrett et al. Lupus. 2016;25:1497-502).

10.7. The Committee noted a clinician application for the use of quinacrine for the treatment of patients with SLE as a second-line substitute for those contraindicated or intolerant to hydroxychloroquine (HCQ), patients not needing corticosteroids with serious fatigue and cognitive impairment, and as an add-on for patients who are partially responsive to HCQ in whom other alternatives are considered inappropriate. The Committee noted that quinacrine is a synthetic drug developed in the 1930s, which was subsequently replaced by chloroquine, and finally HCQ.

10.8. The Committee noted that, in the 2019 update of the European League Against Rheumatism (EULAR) guidelines, the recommendation for the management of SLE was for patients to receive HCQ and glucocorticoids in the first instance, followed if necessary by methotrexate and/or azathioprine for mild to moderate SLE. The Committee noted that HCQ is recommended over chloroquine due to its multiple beneficial effects and possible lower risk for retinal toxicity. The Committee noted that the EULAR recommendation that, in cases of inadequate response or evidence of toxic retinopathy, quinacrine may be used as an add-on or sequential therapy.

10.9. The Committee noted the benefits of HCQ in relief of constitutional symptoms, musculoskeletal manifestations, and muco-cutaneous manifestations of SLE, and that some small randomised trials and observational studies suggest that HCQ may reduce flare rates, thrombotic events, organ damage accrual, and mortality, with an 80% disease remission rate for patients with non-organ-threatening SLE. The Committee noted that HCQ is used for the treatment of patients with SLE in New Zealand, usually at a maximum dose of 5 mg per kg: an average dose of 200 mg per day for the majority of patients.

10.10. The Committee noted that, in the case of SLE skin disease (also referred to as cutaneous lupus erythematosus), approximately 40% of patients will experience insufficient response to first-line treatment with anti-malarial medications (Chasset et al. Br J Dermatol. 2017;177:188-96).

10.11. The Committee noted a case-controlled cohort study of 608 SLE patients, in which deceased SLE patients were matched for disease duration with live patients in a proportion of 3:1, in which the odds ratio for death among patients treated with HCQ was 0.13 (95% CI 0.05 to 0.30), suggesting HCQ has a positive impact on survival for SLE patients (Alarcón et al. Ann Rheum Dis. 2007;66:1168-72).

10.12. The Committee noted that the majority of evidence for the use of quinacrine in the treatment of SLE comes from literature dated from between 1940 and 1960. The Committee noted 4 more recent studies investigating the use of quinacrine in the treatment of SLE:

10.12.1. Toubi et al. Lupus. 2000;9:92-5: case series of six active SLE patients (Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score > 5 points), with a mean duration of illness 9.1 years (range 2 to 17 years) were started on quinacrine (100 mg per day) following failure to achieve clinical remission on a therapeutic regimen which included a maintenance dose of hydroxychloroquine (400 mg daily) together with prednisone (10 to 20 mg/day or higher daily doses of this agent for short periods) and azathioprine (150 mg/day) or methotrexate (7.5 mg/week). The Committee noted that in 5 of the 6 of the patients the addition of quinacrine to the previous treatment was associated with complete remission (SLEDAI 0 to 2 points), which persisted over the follow-up period (mean 2.2 years (range 0.5 to 3.5)). The Committee also noted that 400 mg is a higher dose than the 200 mg per day dose that would usually be prescribed.

10.12.2. Ugarte et al. Lupus. 2018;27:1718-22: a retrospective case series of 46 SLE patients who were unresponsive to treatment with the following drug combinations: hydroxychloroquine + prednisone + immunosuppressive drugs (n=24), hydroxychloroquine + prednisone (n=16), hydroxychloroquine + prednisone + retinoids (n=2), hydroxychloroquine alone (n=1), hydroxychloroquine + one immunosuppressive drug (n=1), hydroxychloroquine + prednisone + one immunosuppressive drug + belimumab (n=1) or hydroxychloroquine + prednisone + belimumab (n=1), who were given quinacrine (either 100 mg/ day or 100 mg/48 hr) for 12 months. The Committee noted that SLEDAI scores decreased significantly from baseline at both 6 months (score reduction of 2.8 points; 95% CI 1.9 to 3.7) and 12 months (score reduction of 3.5 points; 95% CI 2.6 to 4.4). All adverse events experienced were said to be mild and reversible.

10.12.3. Cavazzana et al. Lupus. 2009;18:735-9: a retrospective analysis of 34 patients affected by cutaneous SLE treated with HCQ (5 mg/kg/d) and quinacrine with two regimens: 100 mg (29 cases) and 50 mg (5 cases) The Committee noted that significant improvements with combination therapy were reported for patients with discoid lupus erythematosus (19 cases), acute malar rash (6 cases), chilblain lupus (4 cases) (P=0.009, P=0.019, and P=0.04, respectively).

10.12.4. Chasset et al. Br J Dermatol. 2017;177:188-96: a systematic review and meta-analysis of studies published between 1965 and 2015 to assess the global

cutaneous response rates to HCQ, chloroquine, and quinacrine, with respect to CLE subtypes, based on previously published studies (including Cavazzana et al. 2019).

10.12.5. Members were made aware of an expert perspective article from the American College of Rheumatology on the treatment of refractory cutaneous lupus erythematosus in which places quinacrine directly after HCQ in a suggested treatment paradigm (Borucki R, Werth VP. Arthritis Rheumatol. 2020; online ahead of print).

10.13. The Committee considered that the evidence for the use of quinacrine for SLE was limited, poor quality, and primarily older literature with less rigorous reporting than is currently expected in reporting of treatment studies, or retrospective cohort studies. The Committee considered that it is unlikely any new studies or data on the use of quinacrine for SLE will become available, due to the age of the drug and availability of other, more modern medications. The Committee noted that quinacrine was only used in combination with other therapies, and not as monotherapy, in all of the studies included in the Chasset et al. meta-analysis.

10.14. The Committee noted that compared with HCQ, quinacrine has a faster onset of action (4-6 months vs 2-4 weeks) and less retinal toxicity, but a higher rate of aplastic anaemia, which the Committee considered to be idiosyncratic rather than dose-related. The Committee noted that quinacrine also potentially has a more positive effect on patient fatigue, and SLE related skin issues when compared to HCQ. The Committee considered that funding quinacrine for SLE may lead to an increased expenditure to the health system to monitor for aplastic anaemia, but noted the uncertainty of how often aplastic anaemia occurs, and a lack of comprehensive safety data regarding this.

10.15. The Committee noted that there is no Medsafe approved quinacrine product, however the Committee considered that Medsafe registration is unlikely due to lack of data and commercial viability. The Committee noted that very few clinicians in New Zealand use this agent, and SLE patients usually tolerate HCQ well. The Committee noted that currently, patients for whom HCQ fails would have methotrexate added to their treatment regimen and considered that it is unclear if quinacrine would be used in place of this. The Committee considered the number of patients unable to tolerate methotrexate would likely be small.

11. Biosimilar adalimumab

Application

11.1. The Committee reviewed an application for ABP-501, a biosimilar adalimumab, for use in multiple indications.

11.2. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

11.3. The Committee considered there is no evidence to suggest clinically meaningful differences in the health benefits or risks between reference adalimumab and ABP-501, a biosimilar adalimumab, and **recommended** that PHARMAC could progress a competitive procurement process that resulted in the listing of a biosimilar adalimumab.

11.4. The Committee considered it was clinically acceptable for ABP-501 to be the only available adalimumab product for funded indications, if the cost saving is worthwhile, supply is secured, and adequate implementation support is made available to assist with transition of patients.

Discussion

11.5. The Committee noted that adalimumab, a monoclonal antibody which binds to human tumour necrosis factor alpha (TNFα), is used for a wide range of clinical indications with significant usage within New Zealand and internationally and is associated with a significant portion of pharmaceutical expenditure. The Committee noted that adalimumab is currently (or imminently) funded for rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, plaque psoriasis, hidradenitis suppurativa, Bechet's disease, adult-onset stills disease, pyoderma gangrenosum, and ocular inflammation.

11.6. The Committee noted this discussion was to seek advice on the clinical evidence in support of biosimilar similar adalimumab, specifically ABP-501 (Amgevita), in advance of a possible competitive process for the supply of adalimumab which may seek bids for exclusive supply of adalimumab. The Committee noted that advice regarding implementation considerations relating to the introduction of a biosimilar adalimumab for specific indications had been sought from the relevant Subcommittees.

11.7. The Committee noted the presence of new presentations of adalimumab, including citrate free formulations, and evaluation of widened access to adalimumab, could be considered as part of a biosimilar transition.

11.8. The Committee noted there are eight adalimumab biosimilars, representing five unique products, approved in the EU with a number of biosimilar adalimumab products approved by Medsafe, or currently undergoing Medsafe review. The Committee noted that Amgevita has been approved by the EMA for use in the European Union, by the FDA for use in the United States, by the TGA for use in Australia, and by Medsafe for use in New Zealand for all of the indications of the reference adalimumab product. The Committee discussed the comprehensive international regulatory processes regarding the safety and efficacy of biosimilars, and the process of indication extrapolation of biosimilar products to the reference product.

11.9. The Committee considered it would be appropriate for PHARMAC to seek advice regarding the suitability of any biosimilar adalimumab device prior to a funding decision being made.

11.10. The Committee noted Amgevita is available as a citrate free formulation, with a 27 gauge needle for a 20 mg and 40 mg prefilled syringe and 40 mg prefilled pen.

11.11. The Committee noted that Amgevita is analytically similar with the same primary amino acid sequence, similar structure and strength as the reference adalimumab product, with comparative pharmacodynamic, pharmacokinetic and toxicology data as assessed by the EMA (EMA. Amgevita: EPAR – Public assessment report) and FDA (FDA. Drug approval package: Amjevita(adalimumab-atto)) to determine biosimilarity between Amgevita and Humira. The Committee noted similar biofunctional activity between Amgevita and both the US and EU Humira products had been demonstrated, including testing of the binding kinetics to TNFα kinetics, relative binding to transmembrane TNFα, neutralisation of TNFα induced caspase activation and other demonstrations of functional similarity (Velayudhan J. Biodrugs. 2016;30:339–51).

11.12. The Committee noted a randomised, single-blind, single-dose, three-arm parallel group pharmacokinetic study, investigating pharmacokinetic similarity between Amgevita and Humira (EU and US). The Committee noted the study, conducted in 198 healthy subjects, demonstrated pharmacokinetic data measured over 63 days demonstrated the confidence interval for the geometric mean ratio of AUCinf and Cmax were within pre-specified standard PK equivalence criteria of 0.80 to 1.25 (Kaur, P. Ann Rheum Dis. 2017;76:526-33).

11.13. The Committee noted two phase III studies, one in rheumatoid arthritis (Cohen et al. Ann Rheum Dis. 2017;76:1679–87) and one in plaque psoriasis (Papp K et al. J Am Acad Dermatol. 2017;76:1093–102), demonstrating non-inferiority between Amgevita and reference adalimumab.

11.13.1. The Committee noted the Cohen et al. (2017) trial, consisting of 526 patients treated with either Amgevita (n=264) or US Humira (n=262) reported comparability in the primary end-point, defined as ACR20 response at week 24, with responses of 74.6% (Amgevita) and 72.4% (adalimumab) [90% confidence interval (-0.954 to 1.133)], with safety and immunogenicity comparable between treatment groups.

11.13.2. The Committee noted the Papp et al. (2017) trial, consisting of 350 patients treated with either Amgevita (n=175) or Humira (n=175), noting patients were randomised to treatment, with the primary end point of psoriasis area and severity index (PASI) percentage improvement from baseline, measured at weeks 16, 32 and 50. The Committee noted that patients randomised to Humira treatment were re-randomised at week 16 to switch to Amgevita or continue on Humira through to week 52. The Committee noted PASI percentage improvement from baseline were similar across groups for weeks 16, 32 and 50 (range 85.8 – 88.2%). At week 16, PASI improvement from baseline was 80.8% (Amgevita) and 83.1% (Humira) with changes from baseline similar across groups and time points ongoing, and comparable safety results reported.

11.14. The Committee noted five single switch studies, summarised in Numan et al. Adv Ther. 2018;35:1295-332, reporting the impact on efficacy, safety and immunogenicity of patients switching from Humira to a biosimilar adalimumab throughout a treatment course:

- Cohen et al. Arthritis Res Ther.2019;21:84.
- Cohen et al. Ann Rheum Dis. 2018;77:914-21.
- Hodge et al. Arthritis Rheumatol. 2017;69 (suppl.10), ACR abstract 2879.
- Papp et al. Br. J. Dermatol. 2017;177:1562-74.
- Weinblatt et al. Arthritis Rheumatol. 2018;20:57.

11.14.1. The Committee noted these studies reported comparable efficacy, safety and immunogenicity after a single switch, between treatment arms. The Committee considered these studies indicated comparability in clinical efficacy and safety after switching from reference adalimumab to biosimilar adalimumab, particularly in double-blind studies; however, members noted the impact of apparent nocebo effect (i.e. a negative outcome occurring associated with a belief that the intervention will cause harm) from patients, with relation to the open-label studies.

11.15. The Committee noted two multiple switch studies of patients switching between reference adalimumab and a biosimilar, multiple times:

- Blauvelt et al. American College of Rheumatology meeting abstracts. 2017 ACR/ARHP Annual Meeting. Abstract 2440.
- Genovese et al. Arthritis Rheumatol. 2017;69(suppl.10), ACR abstract 2799.

11.15.1. The Committee noted these studies reported no clinically meaningful differences in long term efficacy, safety and immunogenicity between treatment arms; members noted that these multiple switch studies did not include the Amgevita brand of biosimilar adalimumab.

11.16. The Committee noted there are multiple systematic reviews and commentaries available regarding the comparable clinical effectiveness of several biosimilars in dermatology, rheumatology and inflammatory bowel literature; however, noted they had not seen specific phase III data relating to biosimilar adalimumab use in inflammatory bowel disease, in children, or those using adalimumab for ophthalmologic indications. The Committee noted the ongoing accumulation of real world data supporting use of

biosimilars, and biosimilar adalimumab, and considered that such data did not demonstrate any specific additional concerns across any patient groups.

11.17. The Committee noted the impact of immunogenicity on biologic treatment duration and considered that New Zealand has longer persistence with adalimumab treatment in comparison to other countries. Members speculated whether this is related to the limited number of alternative funded biologics available for some clinical indications. The Committee noted that development of immunogenicity, often diagnosed following the identification of treatment antibodies, leads to loss of treatment effectiveness, and considered that, for most patients, this was part of the inevitable progression of anti-TNF treatment. The Committee considered that there is currently no evidence that the rate of development of immunogenicity differed between reference and biosimilar adalimumab.

11.18. The Committee noted that, whilst there is no evidence that switching between reference and biosimilar adalimumab affects immunogenicity or drug survival, there is risk that any loss in disease control would be perceived due, and attributed to, the switch. The Committee considered this risk was demonstrated through switching studies of other anti-TNFs, where although there have been no meaningful differences in clinical outcomes, adverse events or quality of life reported in double-blind studies, there had been increased patient reports of subjective changes in treatment efficacy and adverse events in open-label switch studies.

11.19. The Committee considered that, based on available evidence, biosimilar adalimumab appears equally effective to reference adalimumab with no evidence to indicate any specific clinical risk or harm with switching from reference adalimumab to a biosimilar. The Committee noted lack of international consensus regarding the interchangeability of biosimilar adalimumab but considered this was likely irrelevant to the New Zealand context where it was likely that only one brand of adalimumab would be listed on the Pharmaceutical Schedule at any one time.

11.20. The Committee considered that the nocebo effect will be a concern with any adalimumab biosimilar and may be attributed to the switch without objective evidence. The Committee considered that the nocebo effect is highly dependent on the prescriber-patient interaction, and that education and clear communication to primary prescribers managing a patient's switch may help reduce this. The Committee considered a range of health professionals are likely to manage a patient switching to a biosimilar, with variation regarding the level of support required dependent on the indication being treated. The Committee considered this would likely involve specialists, general practitioners and pharmacists and noted that the impact any switch would have on these groups should be considered. The Committee considered engagement with patient support groups would also be of value.

11.21. The Committee noted variation in the consequences of loss of treatment response between different indications and considered that for high-consequence indications this may adversely affect patient and clinician confidence in a switch. The Committee considered management of switching patients varied internationally, ranging from grandparenting of existing patients to wholesale enforced switching.

11.22. The Committee considered that, depending on the outcome of a commercial process, further review of the preferred biosimilar adalimumab should be sought prior to a funding decision being made.