PTAC Pharmacology and Therapeutics Advisory Committee

Objective advice to PHARMAC

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Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 14 & 15 November 2019

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
Giles Newton Howes
Jane Thomas
Jennifer Martin
Matthew Strother
Melissa Copland
Sean Hanna
Simon Wynn Thomas
Stephen Munn
Tim Stokes

Apologies
None noted

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:

- Both PTAC and PTAC Subcommittees are statutory advisory committees established by the PHARMAC Board (external to and separate from PHARMAC staff). Both provide objective advice to PHARMAC on community and hospital pharmaceuticals and their benefits, using the PHARMAC Factors for Consideration.

- PTAC considers Applications or PHARMAC staff proposals across all therapeutic groups in the Pharmaceutical Schedule. It has an overview view of Applications and other items referred to it for clinical advice. PTAC provides and promotes critical appraisal of strength and quality of evidence, applied rigorously, systematically and consistently across all therapeutic groups.

- PTAC Subcommittees provide objective advice within specific therapeutic areas. PTAC Subcommittees are separate from, and not subordinate to, PTAC. PTAC Subcommittees are appointed to reflect specialist knowledge and expertise in health needs and treatments within their own therapeutic groups/areas of clinical practice, including the applicability of evidence to clinical funding settings in New Zealand. PTAC Subcommittees make recommendations, including providing a priority, within their therapeutic groups of interest.

- PTAC and PTAC Subcommittees therefore provide separate and different, if complementary, perspectives and advice to PHARMAC. PTAC examines the same evidence with a different perspective from specialist expert PTAC Subcommittees, as do Subcommittees between them.

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.

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

2. Correspondence and Matters Arising

Fomepizole for the treatment of ethylene glycol or methanol poisoning

2.1. The Committee noted that in May 2019, PTAC had considered a funding application for fomepizole in the treatment of ethylene glycol or methanol poisoning.

2.2. The Committee noted that, in May 2019, PTAC had considered that although the evidence base for the use of fomepizole in the treatment of ethylene glycol or methanol poisoning

was poor, there is a high health need in patients with this condition, which disproportionately affects Māori; and the different adverse event profile of fomepizole compared with ethanol may reduce health sector costs in the treatment of these patients.

2.3. The Committee noted that, in May 2019, it had recommended that fomepizole in the treatment of ethylene glycol or methanol poisoning be listed with a high priority. However, the Committee also considered that specialist advice should be sought to further inform assessment of this application and that the priority of its recommendation should be reviewed if further information indicated that fomepizole use would not reduce health sector costs.

2.4. The Committee noted that PHARMAC staff had subsequently sought additional clinical advice from intensive care and emergency physicians regarding the impact fomepizole could potential have on current clinical practice.

2.5. The Committee noted that the specialist clinical advice indicated that, while there may be benefits from the use of fomepizole compared with ethanol given its relative ease of administration, it was considered unlikely there would be any substantive reduction in health resource requirements. This was because there was considerable uncertainty that any patients would not be admitted to ICU irrespective of antidote administered. The Committee noted this was due to the rarity of the presentation of these types of poisonings in each centre, the risks involved particularly with administering an unfamiliar treatment regimen, and the poor evidence base for use of fomepizole in these settings.

2.6. The Committee noted that, in light of this specialist advice, it appears that the funding of fomepizole would not result in a significant reduction of health sector costs at the pricing currently being sought by the supplier.

2.7. The Committee considered that, given the importance of commencing treatment for ethylene glycol or methanol poisoning as soon as possible, hospitals would need to order and hold stock of fomepizole at each centre. The Committee noted that taking into account the shelf-life and rarity of presentation in each centre, a proportion of fomepizole stock holdings would likely expire prior to use. The Committee considered that this represented a significant financial risk for funding of fomepizole and that the cost of expired stock should be factored into any economic assessment of fomepizole.

2.8. Given this additional information, the Committee considered that its priority recommendation regarding fomepizole should be amended. The Committee **recommended** that fomepizole in the treatment of ethylene glycol or methanol poisoning be funded only if cost-neutral to the health sector.

3. Adalimumab & infliximab Drug Monitoring for the treatment of Inflammatory Bowel Disease

Application

3.1. The Committee considered a clinician application for adalimumab and infliximab – therapeutic drug monitoring for the treatment of inflammatory bowel disease (IBD).

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

Recommendation

3.3 The Committee **recommended** that the funding criteria for adalimumab for currently funded inflammatory bowel disease indications be amended to allow for a higher maximum dose (up to weekly dosing as clinically indicated), with a medium priority.

3.4 The Committee **recommended** that the funding criteria for infliximab for currently funded inflammatory bowel disease indications be amended to allow for a higher maximum dose (up to 10mg/kg every 8 weeks or equivalent as clinically indicated), with a medium priority.

3.5 The Committee made these recommendations for adalimumab and infliximab based on the high health need, and evidence of benefit from higher dosing, in patients with inflammatory bowel disease (IBD) who lose response to adalimumab or infliximab.

3.6 The Committee considered that the current evidence for the proposed use of therapeutic drug monitoring (TDM) and measurement of anti-drug antibodies (ADAs) to adjust dosing of adalimumab and infliximab in IBD was insufficient to inform a recommendation. The Committee considered that the funding criteria for adalimumab and for infliximab should be amended to allow use of higher doses of these pharmaceuticals for IBD, with consideration of future opportunities for price reductions with the availability of biosimilar competition and that the criteria could allow (but not mandate) TDM and ADA monitoring or dose modelling to manage dose changes. The Committee considered PHARMAC staff could develop criteria with input from Gastroenterologists if required.

Discussion

3.7 The Committee noted that the Gastrointestinal Subcommittee reviewed this application in October 2018 and had made the following recommendations:

3.7.1 The Subcommittee recommended that the maximum doses set by renewal criteria for gastrointestinal indications for both infliximab and adalimumab be amended to allow higher maximum doses for patients who have undergone therapeutic drug monitoring and where a recent test indicated a higher dose would be beneficial.

3.7.2 The Subcommittee recommended that it would be acceptable to introduce restrictions to renewal criteria for gastrointestinal indications for both infliximab and adalimumab, where such restrictions require therapeutic drug monitoring to be performed and lower the maximum funded dose where test results show this can be done.

3.8 The Committee noted that PTAC reviewed the record of the Gastrointestinal Subcommittee's review of this application in February 2019 and that PTAC did not accept the Subcommittee's recommendations at that time. PTAC had considered that there was evidence to support higher doses in some patients determined by therapeutic drug monitoring (TDM). There was also evidence that some patients may be under-dosed with current restrictions. PTAC had requested PHARMAC staff provide a paper on TDM of biologics for gastrointestinal conditions, and PTAC had highlighted specific concerns regarding uncertainty of benefits and uncertainty of the extent to which the approach would change usage, due to low quality evidence.

3.9 The Committee noted that both adalimumab and infliximab are anti-tumour necrosis factor (anti-TNF) monoclonal antibodies, also called biologic treatments, and that both are Medsafe-approved for use as induction and maintenance treatment of inflammatory bowel disease (IBD). The Committee noted that infliximab is funded for the treatment of Crohn's Disease (CD) and Ulcerative Colitis (UC) and adalimumab is funded for the treatment of CD. The Committee noted that there is increased competition in this market with the introduction of biosimilars, and new monoclonal antibodies with different molecular targets, and that commercial processes may provide opportunities for widening access for these agents.

3.9.1 The Committee noted that adalimumab is funded for use in adults and children with CD and in patients with fistulising CD, with an initial 3 to 6 month induction period that has no dosing restriction, however, the renewal criteria include a maximum dose of no greater than 40 mg every 14 days.

3.9.2 The Committee noted that infliximab is funded for use in adults and children with CD, patients with fistulising CD, patients with severe fulminant UC and patients with severe UC, to be administered at doses up to 5 mg per kg every 8 weeks. The Committee noted that infliximab doses of up to 10 mg per kg every 8 weeks (or equivalent) – treatment re-induction – can be used for up to 3 doses if required for secondary non-response, and that another re-induction may be considered 16 weeks after completing the last re-induction cycle.

3.9.3 The Committee noted that PTAC has previously considered, and PHARMAC has ranked, funding applications for weekly dosing of adalimumab for CD (see Adalimumab for CD, rescue therapy, on the Application Tracker), and for adalimumab for the treatment of UC (see Adalimumab for moderate to severely active UC, first-line and Adalimumab for moderate to severely active UC, second-line, on the Application Tracker).

3.10 The Committee noted that primary loss of response, so-called primary non-response (PNR), occurs in about 10-30% of patients with IBD, where patients do not respond to induction treatment with biologics. Secondary loss of response (LOR) occurs in patients who respond to induction therapy but lose this response during maintenance treatment. Secondary LOR is potentially due to anti-drug antibodies (ADAs), immune mechanisms, and/or inadequate drug concentrations.

3.11 The Committee noted that ADAs may be neutralising, modifying the drug binding site and directly affecting therapeutic response; or non-neutralising, increasing drug clearance through the immune system and thereby leading to reduced therapeutic effect. The Committee noted that a New Zealand study of 103 patients (84 with CD, 17 with UC and 2 with unclassified IBD) who received either adalimumab or infliximab reported that neutralising and non-neutralising ADAs were more common in patients with trough drug concentrations less than 2 mg/L (Barclay et al. Intern Med J. 2019:49;513-18).

3.12 The Committee considered that monitoring disease states is challenging in IBD. Trial-based indices are not used routinely in clinical practice because of concerns about their utility outside randomised controlled trials. Disease assessment for IBD in clinical practice may use any, or all, of: the Crohn's Disease Activity Index (CDAI), endoscopy, testing for C-reactive protein (CRP), and faecal calprotectin.

3.13 The Committee considered that patients with IBD who receive anti-TNF treatment may have a health need due to primary or secondary loss of response to this treatment, as described. Members considered that patients with IBD for whom anti-TNF treatment is not effective may opt to try another biologic agent with a different mechanism of action, although these are not currently funded. Otherwise surgery could be considered. Members considered that optimising anti-TNF treatment may be better than changing treatment or considering surgery for such patients.

3.14 The Committee noted evidence that some patients in New Zealand with IBD already receive higher doses of infliximab than the maintenance dosing of 5 mg per kg every 8 weeks. The Committee considered that use of higher doses may be due to clinician preference, interpretation of the infliximab funding restrictions on the hospital medicines list (introduction and re-introduction), and the practicalities of episodic use in clinics where the remainder of a vial is given to a patient instead of being discarded. Members noted that, until recently, PHARMAC did not have patient level data for infliximab use in DHB hospitals.

3.15 The Committee considered that target concentrations for anti-TNF agents may depend on disease severity, but that the optimal target drug concentrations for adalimumab and infliximab were unclear. Members considered that recommended target concentrations for adalimumab and infliximab in the treatment of IBD have increased with time. However, the Committee considered that there was limited supporting evidence for particular target concentrations.

3.16 The Committee noted that therapeutic drug monitoring (TDM) is a treatment strategy that uses a target drug concentration rather than a target dose. Members noted that TDM may use a variety of dosing strategies including, but not limited to: stepwise dosing, proportional dosing, or model-based dosing. Members considered that it is unclear whether disease symptoms should mediate decisions on drug dosing, or whether use of TDM is a superior strategy in IBD. The Committee noted that TDM is already used around New Zealand for the management of patients who receive adalimumab or infliximab for the treatment of IBD. However, Members noted that uptake of TDM for IBD is not consistent around New Zealand, although has likely increased following the recent publication of New Zealand guidelines (Khan et al. N Z Med J. 2019:132;46-62).

3.17 The Committee considered that TDM strategies may use sequential measurements for dose determination including drug concentration measurement. This can involve eg. dose alteration and concentration re-measurement until therapeutic dose achieved; peak and trough concentration measurement to determine clearance; and then dose determination using other clinical measurements. The Committee noted that dose modelling may be influenced by variables that affect drug concentration. This can include drug clearance, protein breakdown, binding targets, ADAs, disease severity, comorbidities eg. obesity, or other drugs such as methotrexate and glucocorticosteroids.

3.18 The Committee considered that assessment of response in TDM includes some measurements of disease activity that may not be sensitive or specific, eg. CRP, and also technical issues of assay, such as measurement of bound and unbound drug, to best manage this condition. Members considered that, ideally, TDM would use an optimal modelling strategy to measure and promptly reach an optimal target concentration for any given patient with IBD.

3.19 The Committee considered whether the maximum funded doses of adalimumab and infliximab should be increased for the treatment of patients with IBD who are not responding to their current treatment, for either or both of PNR or LOR. The Committee considered that the question of whether a TDM strategy or another mechanism is required to clinically support the rationale for dose escalation and de-escalation was a secondary consideration that did not necessarily need to be determined in the funding criteria for these agents.

3.20 The Committee noted evidence from a double-blind, controlled trial of infliximab maintenance for 54 weeks in 122 biologic-naïve adult patients with active CD who were randomised (1:1:1) to receive either: up to 2 dose increases with steps of 2.5 mg/kg based on clinical symptoms, biomarker analysis and/or serum infliximab concentrations (dose intensification strategy 1, DIS1); a dose increase from 5 to 10 mg/kg based on the same criteria (DIS2); or a dose increase to 10 mg/kg based on clinical symptoms alone (controls) (D'Haens et al. Gastroenterology. 2018:154;1343-51).

3.20.1 The Committee noted the primary outcome of this trial was sustained corticosteroid-free clinical remission (CDAI <150) from weeks 22 through 54 with no ulcers at week 54, and that this was reported to occur in 33% of DIS1 patients, 27% of DIS2 patients, and in 40% of the control group patients (P=0.50).

3.20.2 The Committee noted that reported adverse events (AEs) and serious AEs were similar across all 3 treatment groups and that bowel resections (4), CD-related abscess (2), pancreatitis (5) and infusion reactions (8) were also reported.

3.20.3 The Committee considered that infliximab dose increases, based on symptoms, biomarkers, and serum drug concentration, did not lead to statistically significant differences in proportions of participants with cortisol-free clinical remission, compared to dose increases based on symptoms alone. Members considered this evidence to be of low to moderate quality.

3.21 The Committee noted the report of a retrospective cohort study based on medical record review of 197 paediatric patients (median age 12.6 years) with CD who received adalimumab or infliximab, either when TDM was not available (TDM-) or when TDM was available, where patients had received at least 1 TDM during first-line biologic treatment (TDM+) (Gofin et al. Inflamm Bowel Dis. 2019. doi:10.1093/ibd/izz257 [Epub ahead of print]).

3.21.1 The Committee noted that the primary outcome of this trial was the time to first discontinuation of adalimumab or infliximab, which was reported to be mean 45.0 (standard error (SE), 2.7) months for the TDM+ group compared to mean 33.5 (SE 2.4) months for the TDM- group (P=0.001). The Committee considered that the results of this trial were consistent with TDM being associated with better outcomes with these agents.

3.21.2 The Committee noted that the TDM+ group had a lower rate of hospitalisation per patient per year than the TDM- group (P=0.001) and a higher treatment intensification rate than the TDM- group (P<0.001). The Committee noted that the surgical resection rate was not significantly different between the two groups.

3.22 The Committee noted the following evidence from clinical trials, post-hoc analyses, cohort studies and a pilot study regarding drug monitoring of adalimumab and infliximab in IBD.

- Vande Casteele et al. Gastroenterology. 2015:148;1320-9
- Van Stappen et al. Gut. 2018:67;818-26
- Zittan et al. J Crohns Colitis. 2016:10;510-5
- Adedokun et al. Gastroenterology. 2014:147;1296-1307
- Steenholdt et al. J Crohns Colitis. 2015:9;238-45
- Papamichael et al. J Crohns Colitis. 2016:10;371-2

3.22.1 Members noted evidence from post-hoc analyses reporting disappearance of low-concentration ADAs in some patients with IBD who received dose intensification infliximab (Van Stappen et al. Gut. 2018:67;818-26), and further noted that there is evidence of ADAs becoming undetectable in patients with CD who received infliximab with treatment intensification (Steenholdt et al. J Crohns Colitis. 2015:9;238-45).

3.22.2 Members noted evidence to suggest that increased doses can lead to an increased remission rate (Van Stappen et al. Gut. 2018:67;818-26).

3.23 The Committee noted the treatment paradigm proposed by the New Zealand Society of Gastroenterology Guidelines on Therapeutic Drug Monitoring in Inflammatory Bowel Disease (Khan et al. N Z Med J. 2019:132;46-62). The Committee noted that this guideline suggests TDM in IBD may be cost-saving, may result in fewer disease-related complications, and may reduce the need for surgery. The Committee considered that the guideline is limited by the use of a subjective scoring system, and that the evidence for benefit is largely based on studies reporting retrospective cohort studies. Members noted the limitations with this level of evidence that can bias estimates of efficacy. The Committee also noted that the recommended approach does not cover use of higher drug concentrations, criteria for dose de-escalation, or criteria for treatment cessation. Without the latter, patients could potentially continue on treatment even if it was not providing a benefit.

3.24 The Committee noted that TDM with adalimumab and infliximab for IBD is performed internationally and that this is supported by consensus statements. The Committee noted the following Australian and British guidelines and consensus statements for TDM of adalimumab and infliximab in IBD:

- Mitrev et al. Ailment Pharmacol Ther. 2017;46:1037-53
- Lamb et al. Gut. 2019;68(Suppl 3):s1-s106

3.25 The Committee considered that there is a positive, albeit non-linear, association between higher drug doses and higher exposure to free adalimumab or infliximab. There is also evidence that there is a positive association between treatment outcomes and drug concentrations. However, the extent of the influence of other important clinical characteristics on these relationships is difficult to quantify. The Committee considered that use of higher doses than currently funded to reach higher concentrations of adalimumab and infliximab for IBD were supported by the evidence reviewed. The Committee also noted that there were no head-to-head trials that compared adalimumab to infliximab for the treatment of IBD, and that comparison of the benefits of these two pharmaceuticals is therefore unclear.

3.26 The Committee considered that the evidence base for benefits from TDM in IBD was weak. The Committee considered that TDM was a tool that could offer benefits such as identifying patients who require a higher dose and may help to determine if low drug concentrations are due to ADAs compared to disease severity. The Committee considered that the TDM strategy for IBD proposed by the applicant and in the evidence reviewed fell short of the detailed modelling seen in other TDM strategies. The Committee considered that this TDM approach does not specify appropriate higher doses, facilitate decision-making for treatment cessation, or guide a patient's duration on treatment. Members considered that the proposed TDM strategy could result in unnecessary dose increases for patients with good disease control, if their drug concentrations fell below the TDM-specified threshold.

3.27 The Committee considered that identification of patients who could benefit from higher therapeutic doses could also be done through assessment of response. The Committee also noted that a change in target concentration is known to be required for some patient subgroups eg. intraluminal CD or severe CD phenotypes, where increased drug concentrations are required.

3.28 Members considered that there is unlikely to be an increase in adverse events associated with the use of higher therapeutic doses of adalimumab or infliximab, with or without TDM, due to the target therapeutic dose. Members considered that a reduction in inflammation would benefit patients with IBD by reducing their risk of developing cancer.

3.29 The Committee considered the effect of increased dosing or treatment cessation based on TDM on cost-effectiveness analyses was unclear. This is because there is insufficient evidence to estimate the extent of the incremental benefits. The Committee noted that drug costs would be higher due to increased doses. Members considered that the costs of increased treatment doses may be balanced by reduction in hospital admissions, dose de-escalations and surgeries, however, long-term study data would be needed to better estimate changes to these resource costs. Members considered that cost-savings could result from a reduction in surgery if there was a substantial increase in remission rates, and from treatment cessation in patients who were not receiving a benefit from adalimumab or infliximab. The Committee considered that it was unclear whether patients who previously used and discontinued biologic treatment for IBD would receive this treatment again.

3.30 The Committee considered that resource requirements for clinic assessments, laboratory tests, patient monitoring and physician training would be the same as those currently required, because TDM is currently used for management of IBD in NZ. The Committee noted that drug concentration and ADA tests are performed only in Christchurch with a reasonable turnaround time of 4 weeks, however, it was unclear which drug form(s) are measured eg. unbound, bound and/or total. Members considered that it was uncertain whether one laboratory could sufficiently perform testing for all NZ IBD patients if required. However, it seemed likely that turnaround times would be appropriate for long-term monitoring for disease management. Members considered that close monitoring may provide a benefit with regard to patient adherence with treatment, and that TDM could help rationalise the use of other pharmaceuticals.

3.31 The Committee considered that the current evidence for the proposed use of TDM and measurement of ADAs to adjust dosing of adalimumab and infliximab in IBD was insufficient

to inform a recommendation. The Committee noted that PHARMAC's role is not to specify management but to fund medicines for the benefit of patients with a health need. The Committee considered that the funding criteria for adalimumab and for infliximab should be amended to allow use of higher doses of these pharmaceuticals for IBD, and that the criteria could allow (not mandate) TDM or dose modelling based on specific guidelines.

3.32 The Committee considered that the amended funding criteria would apply to patients with PNR for whom dose adjustment would be justified, and to those with LOR who may have ADAs and for whom dose adjustment may be appropriate in some cases. The Committee considered that the funding criteria could be simplified to allow escalation of doses to reach therapeutic levels, and criteria to state that dose escalation should not be performed in patients with therapeutic drug levels (who are being adequately treated) or patients with high levels of neutralising ADAs (who would not receive any further benefit from the drug). The Committee considered that PHARMAC staff could develop criteria with input from Gastroenterologists if required.

3.33 The Committee considered that TDM strategies may be applicable to treatment with adalimumab or infliximab in other indications, although evidence for other indications was not considered at this time due to the focus of this application for the treatment of IBD, however, evidence regarding the use of TDM in other indications could be considered at future meetings.

4 Tacrolimus suppositories for the treatment of treatment-refractory rectal inflammation

Application

4.3 The Committee reviewed the clinician application for tacrolimus suppositories for the treatment of treatment-refractory rectal inflammation in patients with inflammatory bowel disease (IBD).

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

Recommendation

4.5 The Committee **recommended** that the application for tacrolimus suppositories for the treatment of rectal inflammation be declined, based on the lack of a proprietary tacrolimus suppository product, and due to uncertainty around the quantity and quality of evidence for use of tacrolimus suppositories compared with other tacrolimus preparations and compared with other pharmaceuticals**.**

4.6 The Committee suggested that the Gastrointestinal Subcommittee review and consider the application for tacrolimus suppositories for the treatment of treatment-refractory rectal inflammation; and in particular, seek comment on the randomised controlled trial investigating tacrolimus suppositories compared to beclomethasone suppositories in patients with 5-aminosalicylate refractory ulcerative colitis (Lie et al. Clin Gastroenterol Hepatol. 2019. DOI: 10.1016/j.cgh.2019.09.049 [epub ahead of print]).

Background

4.7 The Committee noted the history of the application for tacrolimus suppositories for treatment-refractory rectal inflammation in patients with IBD, which was received by PHARMAC in September 2017:

4.7.1 In October 2018, the Gastrointestinal Subcommittee considered the application and recommended that tacrolimus suppositories be funded without restriction with a high priority. The Gastrointestinal Subcommittee considered that while the scope and quality of the clinical evidence was limited, the studies did show

efficacy. The Gastrointestinal Subcommittee considered that there is significant morbidity in the patient population with rectal inflammation due to IBD, that medications such as budesonide and other topical agents do not seem to be effective, and that tacrolimus suppositories might potentially reduce the need to escalate to biologics.

4.7.2 In February 2019, PTAC considered the application for tacrolimus suppositories and considered that it was unclear what the costs of this proposal would be, as a process for compounding and distributing tacrolimus suppositories had not yet been developed. PTAC considered that more information was needed to provide advice about this application and so did not accept the Gastrointestinal Subcommittee's recommendation. PTAC recommended that PHARMAC research the costs of providing tacrolimus suppositories and bring this information to PTAC for a recommendation about priority for funding.

Discussion

4.8 The Committee noted that tacrolimus is a macrolide calcineurin inhibitor that acts as an immunomodulator, reducing cytokine levels and reducing damage from immune responses.

4.9 The Committee noted that PHARMAC currently funds oral tacrolimus capsules for organ transplant and for patients who require long-term immunosuppression where ciclosporin has been trialled and discontinued.

4.10 The Committee considered that patients with rectal inflammation due to IBD have a high health need due to the chronic nature of this disease, especially the small proportion of patients who have not responded to previous treatment and experience disabling proctitis. Members considered that the current treatment options for these patients are the anti-tumour necrosis factor inhibitors (anti-TNFs) adalimumab and infliximab, which are funded for more severe cases of IBD where other treatments have failed. Adalimumab is not currently funded for ulcerative colitis (UC). If there is insufficient response to anti-TNFs then subsequent treatment would be surgical removal of the colon.

4.11 The Committee noted that the application for tacrolimus suppositories is for the treatment of patients with IBD that is localised to the rectum; specifically, those with UC of the rectum (ulcerative proctitis) or distal colitis, and those with IBD for whom first- and second-line therapy with oral and topical mesalazine and corticosteroid preparations have not been effective. The Committee noted that the Gastrointestinal Subcommittee estimated had that approximately 300 patients per year may be eligible for treatment with tacrolimus suppositories according to these patient definitions. The Committee considered that a total of about 50 patients nationwide per year may be a more realistic estimate of patient numbers.

4.12 The Committee considered that topical treatment of proctitis, such as tacrolimus suppositories in patients for whom mesalazine and steroids has not been effective, may delay or prevent use of the anti-TNFs adalimumab and infliximab. The Committee considered that infliximab may be an appropriate comparator for assessment of the efficacy of tacrolimus suppositories in the requested patient population.

4.13 Members were of the view that topical treatment, eg. with suppositories, exerts a local effect due to high drug concentrations within the bowel wall. However, Members considered that the drug could also be acting systemically because of rectal mucosal absorption to systemic circulation. The Committee advised that there is some literature regarding the use of oral tacrolimus in IBD but there appears to be little medical interest in further investigating this treatment modality, and noted that there are no comparative studies comparing rectal to oral dose regimens of tacrolimus in IBD.

4.14 The Committee noted the evidence from the randomised, double-blind, placebo-controlled, induction trial of topical tacrolimus 0.5 mg/mL ointment, 3 mL twice a day for eight weeks in 21 adults with active UC with inflammation limited to 25 cm from the anal verge (Lawrence et al. Clin Gastroenterol Hepatol. 2017;15:1248-55). The Committee noted the trial used an ointment preparation with applicator (not a suppository), that it included an adult population with established UC, and that the trial was conducted at four centres in Australia. The Committee noted that all patients had received insufficient benefit from or did not tolerate conventional therapy with either oral and/or rectal mesalazine and/or oral or rectal steroids, and that the proportions of patients in each treatment group who were intolerant of, or received insufficient benefit from, these agents was similar.

4.15 The Committee noted that the primary endpoint of this randomised induction trial was clinical response at 8 weeks follow-up, and that the authors reported that 8 of 11 patients receiving tacrolimus achieved clinical response demonstrated by the Mayo Clinic score, compared with 1 of 10 patients receiving placebo (73% vs 10%; *P*=0.004). The Committee noted that five patients receiving tacrolimus achieved clinical remission compared with no patients receiving placebo (45% vs 0%; *P*=0.015) and that mucosal healing was achieved in eight patients receiving tacrolimus compared with one patient receiving placebo (73% vs 10%; *P*=0.004). The Committee noted that the trial stopped after a planned interim analysis due to the large statistically and clinically significant differences observed between the groups.

4.16 The Committee noted that quality of life outcomes in this randomised induction trial were measured using the Inflammatory Bowel Disease Questionnaire (IBDQ) and that the authors reported increases in IBDQ score of 16 or more points over baseline in five patients who received tacrolimus compared to two patients who received placebo (45% vs 20%, *P*=0.36).

4.17 The Committee noted that the authors of this randomised induction trial reported that there were no safety issues (such as serious infections, hospitalisations, anaphylaxis or serum sickness) identified with the rectal use of tacrolimus ointment. The Committee noted that there was no statistically significant association in the trial between tacrolimus trough levels and clinical outcomes, and no association between tacrolimus trough levels and side effects.

4.18 The Committee considered that the evidence from this randomised induction trial suggested that rectal tacrolimus ointment is more effective than placebo for induction of a clinical response in patients with resistant ulcerative proctitis, however, the trial did not provide evidence of long-term efficacy or safety.

4.19 The Committee also noted the following evidence from non-experimental studies for tacrolimus ointment or suppositories but considered the evidence to be of low quality:

- A prospective pilot study of topical tacrolimus 0.3 mg/mL ointment, 3 mL twice a day for eight weeks in eight adults with UC proctitis uncontrolled by 5-aminosalicylic acid, steroids, immunosuppressants, and infliximab (Lawrence & Copeland. Aliment Pharmacol Ther. 2008;28:1214-20).

- A phase I study of 2-4 mg tacrolimus enema or 2 mg suppository for four weeks in 19 patients with left-sided colitis or proctitis, refractory to local steroids alone or with 5-aminosalicylates (van Dieren et al. Inflamm Bowel Dis. 2009;15:193-8).

- A retrospective analysis of 43 patients with distal UC refractory to combined topical and systemic treatment who received 2 mg tacrolimus suppositories twice daily as add on medication (Jaeger et al. Inflamm Intest Dis. 2019;3:116-24).

4.20 Members noted the above November 2019 article in-press (Lie et al. Clin Gastroenterol Hepatol. 2019. [epub ahead of print]) which reported the results of a small, short-term randomised controlled trial investigating tacrolimus suppositories compared to

beclomethasone suppositories in patients with 5-ASA refractory UC. Members considered that the patient population included in the brief reporting of this study were resistant to previous treatments, and that the study appeared to be of higher quality than the other currently available evidence. Members noted that the study indicated equivalent clinical and endoscopic responses at 4 weeks with tacrolimus compared with beclomethasone, with no significant differences in adverse event rates. The Committee was of the view that the impending full publication of this trial may provide useful evidence and should be considered by the Gastrointestinal Subcommittee; however, the Committee considered that the appropriate comparator would be infliximab rather than beclomethasone suppositories.

4.21 Members noted recent guidance from the American College of Gastroenterology (Rubin et al. Am J Gastroenterol. 2019;114:384-413) regarding the induction of remission in mildly active UC, which did not make any recommendation regarding tacrolimus for the treatment of UC in adults. Members noted that the evidence for tacrolimus that was referenced in this guidance comes from three trials of oral tacrolimus that were either single-arm or placebo-controlled and that the reviewers considered there was limited data regarding long-term outcomes and colectomy rates.

4.22 Members noted that National Institute for Health and Care Excellence (NICE) guideline for management of UC (NICE guideline NG130 [Internet]. NICE (UK); May 2019) did not make any recommendation regarding the use of tacrolimus for UC. Members noted that the evidence for tacrolimus that was referenced in the NICE guidance came from the randomised controlled trial of tacrolimus ointment reported by Lawrence et al. described above, which NICE considered to be of low quality, and NICE had expressed concerns about the applicability of the evidence due to the ointment preparation used instead of a suppository.

4.23 The Committee noted that the NICE guideline NG130 included a cost-effectiveness analysis of treatments for induction of remission in mild to moderate UC, and reported that fourth-line use of topical tacrolimus for proctitis may be cost-effective but the health gains in quality-adjusted life years would be small due to the small number of patients who require fourth-line treatment in the UK. The Committee noted that the NICE reviewing committee did not recommend topical tacrolimus given the uncertainty around treatment sequencing and the cost of compounding suppositories, instead making a research recommendation to further investigate efficacy and cost-effectiveness of topical tacrolimus for treatment-resistant proctitis.

4.24 The Committee considered that there remained uncertainty around the quantity and quality of evidence for use of tacrolimus suppositories, compared with for other tacrolimus preparations and for other pharmaceuticals**.**

4.25 The Committee noted that, in October 2018, the Gastrointestinal Subcommittee had noted that the compounding of suppositories was challenging and that most community pharmacies do not have the capability to compound suppositories. The Committee noted that there is no proprietary tacrolimus suppository product and that compounding of tacrolimus suppositories would need to be outsourced, which would be associated with significant cost compared to the cost of the tacrolimus itself.

5 Subcommittee Records

Cancer Treatment Subcommittee

5.3 The Committee noted the record of the Cancer Treatments Subcommittee of PTAC held on 5 July 2019.

5.4 In regards to item 2, vismodegib for the treatment of locally advanced or metastatic basal cell carcinoma (BCC), the Committee noted that CaTSoP had recommended funding for patients with metastatic or locally advanced BCC where surgery and/or radiation therapy are not appropriate with medium priority, subject to Special Authority criteria.

5.5 The Committee noted that CaTSoP considered where patients are not amenable to surgery or radiotherapy, there were limited treatment options; for many patients the only treatment option was palliative care, as they would not be fit enough for chemotherapy due to age or poor health status.

5.6 The Committee also noted that while CaTSoP had proposed a Special Authority criteria with a view to defining a population that would benefit most from vismodegib treatment, CaTSoP had also indicated there would likely be a significant fiscal risk associated with funding of vismodegib, related to the difficulty in being able to clearly and appropriately define a population for whom surgery, radiotherapy or other chemotherapy are contraindicated or inappropriate. The Committee shared CaTSoP's concerns regarding the difficulties with population definition and the associated potential risk of use of vismodegib beyond the intended population. Members considered this would likely be due to both variation in interpretation of the proposed Special Authority criteria and, as CaTSoP had identified, a preference for using vismodegib instead of surgery/radiotherapy should vismodegib be funded.

5.7 The Committee noted that in practice, vismodegib may be used with alternate dosing regimens to those in the primary clinical trial evidence, such as intermittent dosing schedules with the aim of reducing toxicity. The Committee noted that evidence for use of alternate dosing approaches was poor, coming solely from anecdotal case reports.

5.8 The Committee noted that PTAC had previously considered the application for vismodegib at its meetings in May 2015 and February 2018. At these meetings, PTAC had considered the evidence for the use of vismodegib in the treatment of locally advanced or metastatic BCC was of weak strength and quality, use was associated with significant toxicities, it was a high-cost medicine, and PTAC had recommended that funding of vismodegib for BCC patients be declined.

5.9 The Committee noted the Subcommittee's careful consideration and advice about vismodegib. However, based on the difficulties objectively defining the clinical population eligible for the treatment should it be funded; the high level of fiscal and clinical risks associated with the use of this agent in a clinical population with less extreme disease manifestations; the limited evidence base; and finally the very high price sought by the supplier; the Committee did not consider that its previous recommendation regarding the funding of vismodegib should be changed.

5.10 In regards to item 4: evidence appraisal discussion, the Committee appreciated the useful way in which CaTSoP considered these issues. The Committee considered that CaTSoP's discussion highlighted well the issues and increasing complexity associated with critical appraisal of clinical trial evidence that PTAC, CaTSoP and other clinical advice committees were dealing with. **[Withheld]**

5.11 In regards to item 5; cetuximab and bevacizumab for treatment of metastatic colorectal cancer (CRC) left-sided CRC and bevacizumab right-sided CRC, the Committee noted that CaTSoP had recommended that cetuximab for the first-line treatment of left-sided metastatic colorectal cancer be funded with a medium priority subject to Special Authority criteria.

5.12 The Committee noted that the application for cetuximab for the first-line treatment of RAS wild-type, left-sided metastatic CRC was reviewed by PTAC in August 2018; and recommended for decline. The Committee also noted that in August 2018, PTAC had also referred the application for advice from CaTSoP regarding EGFR-inhibition in mCRC, including for anatomically defined sub-populations.

5.13 The Committee noted that CaTSoP had considered that mutations in EGFR, RAS, and BRAF are widely accepted as prognostic and predictive markers in CRC, and that primary tumour location, or 'sidedness' has been recognised as a prognostic factor in mCRC for

some time, but that it has only recently been suggested that 'sidedness' may also be predictive of response to treatment.

5.14 The Committee acknowledged that there did appear to be a biologic rationale for a differential response to treatment by tumour location; and that it was highly unlikely that prospective trial data investigating this would be forthcoming.

5.15 The Committee noted that CaTSoP had considered that although the data for the use of cetuximab in left-sided mCRC is largely from post hoc analyses, that the signal of a benefit is consistent that cetuximab provides a moderate survival benefit for patients with RAS and BRAF wild-type, left-sided mCRC with manageable toxicity and no significant effect on quality of life.

5.16 The Committee considered that there was a strong risk of bias in data from retrospective post-hoc meta-analysis of multiple big trials. The Committee considered that the body of evidence for cetuximab in the requested population reported only a minimal benefit, particularly when viewed in the context of other cancer treatments that provided more than 12 months of survival gain or the health benefits seen from treatments for some non-cancer indications. The Committee considered that given this small benefit, and taking into account the current pricing sought by the supplier, the cost-effectiveness of cetuximab for RAS and BRAF wild-type, left-sided mCRC would likely be poor.

5.17 The Committee acknowledged and appreciated the Subcommittee's careful consideration and advice regarding cetuximab. However, the Committee did not consider that its previous recommendation regarding the funding of cetuximab for mCRC should be changed.

5.18 The Committee noted and agreed with the Subcommittee's recorded considerations and recommendations regarding the remaining items of the July 2019 meeting.

5.19 The Committee noted again that PTAC and PTAC Subcommittees may differ in the advice they provide to PHARMAC, due to their different, albeit complementary, roles, expertise, experience, and perspectives; and that PHARMAC would take into consideration both committees' points of view in its assessment of these applications.

6 Biosimilar Update

Discussion

6.3 The Committee noted a presentation from PHARMAC staff providing an update on biosimilar commercial processes that are currently underway or in the planning stages. The Committee noted that PHARMAC had recently consulted on a proposal to list a biosimilar rituximab (Riximyo, supplied by Novartis) from 1 March 2020. Riximyo would be the only funded brand of rituximab for all funded indications excluding rheumatoid arthritis. Members noted the proposal would widen access to a range of indications and release significant funds for PHARMAC to invest in other medicines. Members noted that there would be further opportunity to review the current funded indications for rituximab to assess if other changes could be recommended in the future.

6.4 The Committee noted that the Cancer Treatments Subcommittee (CaTSoP) had recently reviewed data for Riximyo, and had considered: the non-clinical physicochemical and pharmacology data and clinical trial data clearly demonstrated biosimilarity of Riximyo with reference rituximab, with all measures of efficacy and adverse events appearing indistinguishable; given physiochemical and functional comparability there was no reason to believe there to be any clinical risk with changing to biosimilar rituximab; the clinical evidence for comparability is of good quality and supports the use of Riximyo for all funded indications; no evidence to suggest any differences in the health benefits or risks obtainable with the Riximyo and Mabthera brands of rituximab. The Committee noted that CaTSoP had concluded that it would be clinically acceptable for Riximyo to be listed and be the only

available rituximab product for all funded indications, if the cost saving is worthwhile and supply is secured.

6.5 The Committee noted that PHARMAC continues to develop its approach to encourage biosimilar entry and to determine the commercial process that is appropriate for each biologic. The Committee considered that PHARMAC staff should determine when to seek clinical advice from PTAC or its Subcommittees for each biosimilar and that this may vary depending on the situation. Members considered that it is important to continue to involve Subcommittees in the review of biosimilars where appropriate and practical, to increase awareness and support for any changes.

7 Sirolimus widening access to include lymphovascular malformations

Application

7.3 The Committee reviewed a clinician application for oral sirolimus for the treatment of lymphovascular malformations.

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

Recommendation

7.5 The Committee **recommended** that oral sirolimus for the treatment of severe non-malignant lymphovascular malformations be funded with a high priority.

7.5.1 The Committee made this recommendation based on the high health need of patients with non-malignant vascular malformations, the limited effective and acceptable standard treatment options, and the benefit of sirolimus on disease management through lesion shrinkage and quality of life improvement.

7.5.2 The Committee considered that widening access to sirolimus for this indication is appropriate as there is an identifiable patient population with lymphovascular malformations currently funded via the Named Patient Pharmaceutical Assessment (NPPA) pathway, and listing may help to ensure ongoing supply of sirolimus for suitable patients and alleviate the administrative burden for clinicians.

7.6 The Committee considered that sirolimus for the treatment of lymphovascular malformations should be listed subject to the following Special Authority criteria:

Initial application – (severe non-malignant lymphovascular malformations)
Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. Patient has severe non-malignant lymphovascular malformation; and
2. Any of the following:
    2.1 Malformations are not adequately controlled by sclerotherapy and surgery; or
    2.2 Malformations are widespread/extensive and sclerotherapy and surgery are not considered clinically appropriate; or
    2.3 Sirolimus is to be used to reduce malformation prior to consideration of surgery; and
3. Patient is being treated by a specialist lymphovascular malformation multi-disciplinary team; and
4. Patient has measurable disease as defined by RECIST version 1.1 (see Note).

Renewal – (severe non-malignant lymphovascular malformations)
Approvals valid for 12 months for applications meeting the following criteria:
1. Patient's disease has had either a complete response or a partial response to treatment, or patient has stable disease according to RECIST version 1.1 (see Note); and
2. Either:
    2.1 Response to treatment in target lesions has been determined by radiologic assessment (CT or MRI scan) following the most recent treatment period; or
    2.2 Both:
        2.2.1 Patient has measurable disease as defined by RECIST version 1.1; and
        2.2.2 Patient's disease has not progressed clinically and disease response to treatment has been clearly documented in patient notes; and

3. No evidence of progressive disease according to RECIST criteria (see Note); and
4. The treatment remains clinically appropriate and the patient is benefitting from the treatment.

Notes: Baseline assessment and disease responses to be assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (Eisenhauer et al. Eur J Cancer 2009;45:228-47

Discussion

7.7 The Committee noted that sirolimus is a T cell inhibitor which forms a complex that inhibits the mTOR pathway, blocking several signal transduction pathways including the PI3K/AKT pathway, leading to inhibition of lymphocyte activation and increased immunosuppression.

7.8 The Committee noted that sirolimus is Medsafe-approved for prophylaxis of organ rejection in patients at mild to moderate immunological risk receiving renal transplants, and that it is listed in the Pharmaceutical Schedule as rescue therapy for an organ transplant recipient. Members considered that sirolimus use for transplant recipients represents a small patient group and that patients funded via NPPA for other uses represent a reasonable portion of its funded use.

7.9 The Committee noted that PHARMAC has previously considered funding of sirolimus for individual patients for the treatment of lymphovascular malformations secondary to different underlying conditions (such as Klippel-Trenaunay Syndrome (KTS), Blue Rubber Nevus, Gorham-Stout disease and lymphatic malformation) through the Named Patient Pharmaceutical Assessment (NPPA) pathway.

7.9.1 [Withheld]

7.9.2 The Committee noted that patients considered under NPPA typically had lesions throughout the abdomen, pelvis, lower limbs and cervicofacial areas resulting in deformity, bleeding, pain and difficulties with movement, swallowing and/or breathing.

7.9.3 The Committee noted that the patient group considered for funding through NPPA is expected to represent less than 10 patients per year, being those with extensive and severe disease, with a history of sclerotherapy and/or previous debulking procedures, and lesions not considered amenable to further surgery.

7.10 The Committee noted that the applicant estimates less than 5 patients per year would be suitable for treatment with sirolimus for lymphovascular malformations. The Committee considered that lymphovascular malformations are rare and considered that patient numbers would be highly dependent on disease definitions used. Members noted that Starship Children's Hospital in Auckland facilitates regular multi-disciplinary meetings where cases of lymphovascular malformations are discussed.

7.11 The Committee noted that current genotypic definitions (eg. identifiable somatic or germline PIK3CA signalling pathway mutation) and phenotypic definitions (eg. patient did not receive a response from prior therapies) are not mutually inclusive and are unable to accurately define all patients with lymphovascular malformations, such as some patients assessed via NPPA. Members considered that patients with lymphovascular malformation are difficult to define but clinically recognisable.

7.11.1 Members considered that this genotypic definition may include patients beyond the intended group, because PI3K mutation is common. Members noted that PI3K mutation would likely be detected in between 20% to 50% of patients with lymphovascular malformations according to variable phenotypic definitions.

7.11.2 Members considered that patients with Kaposiform Haemangioendothelioma, Blue Rubber Bleb Naevus Syndrome and other lymphovascular malformations (entities described as PIK3CA-Related Overgrowth Spectrum (PROS) by

Keppler-Noreuil et al. Am J Med Genet A. 2015;167A(2):287-95) should be considered within this population.

7.11.3 The Committee considered that the common characteristics of the applicant-defined patient groups were lesions arising from lymphovascular tissue and occurrence in children.

7.12 The Committee noted that current treatment options for lymphovascular malformations include observation, sclerotherapy, symptomatic management, laser therapy and surgical options such as debulking and/or total resection. However, some of these interventions may have limited benefit, result in scar tissue and can lead to regrowth of lesions. Members considered that lymphovascular malformations can present an airway risk, making intubation for surgical treatment not feasible.

7.13 The Committee noted that surgical debulking is not appropriate for patients with widespread/extensive malformations, and although surgical management addresses the consequence of lymphatic malformation it has no impact on the underlying cause, with patients typically requiring several surgeries. The Committee noted that risks of surgical debulking include cosmetic deformity, fistula formation, vascular damage and nerve injury.

7.14 The Committee considered that patients with lymphovascular malformations were a broad, varied group with a high health need, although the specific health need of individuals would depend on the location, size and rate of change of lesions. The Committee noted evidence that patients with vascular malformations have lower quality of life (QOL) scores for physical, body pain, social functioning and mental health domains compared to the general population (Nguyen et al. JAMA Dermatol. 2018:154;661-9). Members considered that family members of patients with lymphovascular malformations would have a health need due to stress associated with a chronically ill child or family member.

7.15 The Committee noted that the primary evidence submitted by the applicant was a phase II, open-label study investigating the efficacy and safety of sirolimus (0.8 mg/m^2 twice daily, guided to target trough levels of 10-15 ng/ml) for complicated vascular anomalies (Adams et al. Pediatrics. 2016;137(2):e20153257). The Committee noted that the study included 57 patients aged 0 to 31 years with a diagnosed vascular anomaly and at least 1 of 6 predefined complications.

7.15.1 The Committee noted that the primary endpoint of this study was response according to an aggregate of clinical criteria and functional impairment, quality of life (QOL), and radiologic assessment using either the Response Evaluation in Solid Tumour (RECIST) criteria or modified RECIST.

7.15.2 The Committee noted that, although no participants had a complete response, 85% had a partial response at the end of course 12 (each course defined as 28 days) (Adams et al. 2016). Members considered this aggregate primary endpoint was useful although it is a non-validated, study-specific measure.

7.16 The Committee noted other evidence from retrospective and prospective reviews. Each of these reports involved 20 or fewer participants with lymphatic anomalies/lymphovascular malformations and reported a surrogate of response rate (RR) to sirolimus, usually defined by RECIST, which varied from 50% to 80% or higher (Ricci et al. Pediatr Blood Centre. 2019;66: :e27614, Ozeki et al. Orphanet J Rare Dis. 2019;14:141, Triana et al. Eur J Pediatr Surg. 2017;27:86-90).

7.17 The Committee noted a retrospective review of 19 patients treated with sirolimus for cervicofacial lymphovascular malformation, which reported that 6 patients developed cellulitis and 4 patients had bleeding throughout treatment (Strychowsky et al. Laryngoscope. 2018;128:269-76). The Committee noted that 12 patients stopped sirolimus therapy and of these, 7 experienced recurrence of symptoms and resumed treatment.

7.18 The Committee considered that the evidence for sirolimus supports a tumour-shrinking effect, however, the optimal duration of treatment and whether therapy should be ongoing or intermittent remains unknown.

7.19 Members considered that some adverse effects (AEs), eg. bleeding and thrombotic events, occur soon after treatment and are likely reported in the evidence, however, long-term AEs such as ulceration, hemiplegia or organ impacts may occur over a much longer period eg. 10 to 15 years, and would not be evident in the available evidence.

7.20 The Committee noted that the safety profile of sirolimus includes AEs such as bleeding, thrombosis, delayed wound healing, skin malignancies, hypersensitivity, infections, hyperlipidaemia, renal insufficiency and proteinuria (Rapamune Data Sheet. Medsafe [Internet]. 2012 [Updated September 2019]). Members considered that suppression of platelets in the bone marrow can occur with sirolimus, eg. when used in bone marrow transplant patients, and trough drug concentration monitoring may be required. The Committee noted that the Medsafe data sheet states blood trough concentrations of sirolimus are generally maintained between 4-12 ng/mL (for transplant indication) and that co-treatment with medicines with CYP3A interactions should be avoided where possible, otherwise additional monitoring of drug levels may be required.

7.21 The Committee noted a prospective review of 20 patients receiving sirolimus for lymphatic abnormalities that reported a statistically significant improvement in QOL (p=0.0105) from pre-treatment to 6 months in the entire patient cohort (Ozeki et al. 2019), and a retrospective review of 18 patients receiving sirolimus for generalised lymphatic anomaly and Gorham-Stout disease that reported a QOL improvement in 78% of patients (Ricci et al. 2019). The Committee noted that the quality of life (QOL) data for sirolimus in the treatment of lymphovascular malformations generally comes from uncontrolled reviews and case reports that use a variety of measurement tools.

7.22 The Committee noted that the available evidence does not report decreases in disease-related adverse events (AEs) and that the focus of the evidence was lesion size. The Committee considered that the evidence was of poor to moderate quality, and was subject to inevitable bias due to the limitations of their study methods, coming primarily from individual case reports, including publication bias. The Committee considered that there is a strong biologic rationale for use of sirolimus in the treatment of lymphovascular malformations in patients with molecularly defined disease, however, there is no evidence from prospective clinical trials designed to investigate its use in this patient population.

7.23 The Committee considered that the available evidence suggests treatment that results in a response improves QOL in patients with lymphovascular malformations.

7.24 The Committee considered that sirolimus would likely offer benefit to patients who have already undertaken local therapies such as surgery and sclerotherapy, however, sirolimus may be used earlier in treatment. Members considered sirolimus may be preferable to invasive treatment options eg surgical debulking; however, members considered that sirolimus may simply be used earlier in the treatment paradigm for the same patient population, resulting in no increase to the patient numbers receiving sirolimus.

7.25 Members considered that tumour shrinkage with sirolimus may facilitate anaesthesia and future sclerotherapy in patients, and that pre-operative treatment with sirolimus for malformation reduction could also lead to better outcomes after surgery, especially in children.

7.26 Members considered that the fiscal risks associated with funding sirolimus for the treatment of lymphovascular malformations were small, given its limited use in organ transplant recipients and known adverse effects, and considered that the risk of use in patients out of scope of the Special Authority criteria was small.

7.27 The Committee considered that the funding of sirolimus may require additional testing and visits (for therapeutic drug monitoring and toxicity monitoring), and prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP) with twice-weekly cotrimoxazole. Members considered that if a genotypic definition were used for Special Authority criteria, an additional biopsy and molecular testing may be required.

7.28 The Committee considered that the dynamic, evolving patient group with lymphovascular malformations could not be accurately defined based on current evidence and considered that the definition of this patient group would change over time as more data becomes available. The Committee considered that a pragmatic population definition of lymphovascular malformation based on clinical phenotype and failure to respond adequately to prior therapies could be suitable to use for funding criteria, and that a requirement for genetic testing was not a suitable criterion based on current evidence.

7.29 The Committee considered that a refined definition of the appropriate patient population and a specific outcome, such as the aggregated response outcome used by Adams et al. 2016 or a response based on conventional RECIST assessment, should be used to model cost-effectiveness. Members noted that RECIST assessments are challenging to perform in clinical practice due to resource requirements and complexity. Members considered that RECIST assessments may be performed informally, which could result in difficulties auditing compliance with funding restrictions.

7.30 The Committee commented that this had been a complex and challenging application to consider, further complicated by some overlap in the scope of funding considerations for medicines for rare disorders with limited evidence, and the need to define eligible populations suitable for the Pharmaceutical Schedule.

8 mTOR inhibitors for the treatment of renal angiomyolipoma and refractory seizures associated with Tuberous Sclerosis Complex

Application

8.3 The Committee reviewed clinician and consumer applications for mTOR inhibitors (everolimus and sirolimus) for the treatment of renal angiomyolipoma, and refractory seizures, associated with Tuberous Sclerosis Complex.

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

Recommendation

8.5 The Committee **recommended** that an mTOR inhibitor be funded for the treatment of clinically significant complications resulting from tuberous sclerosis complex (TSC) with a medium priority.

8.5.1 The Committee made this recommendation based on the unmet health need for patients with clinically significant complications from TSC and the moderate evidence of benefit from mTOR inhibitors including quality of life improvement for people with clinically significant complications of TSC. The Committee also acknowledged the low to moderate quality of the available evidence and noted that the evidence base for everolimus was more robust that that for sirolimus.

8.5.2 The Committee considered the clinical effectiveness of mTOR inhibitors in this indication was a class effect and therefore either everolimus or sirolimus could be considered for funding, depending on fiscal risk and commercial arrangements.

8.6 The Committee **recommended** that an mTOR inhibitor be funded for the treatment of refractory epileptic seizures resulting from tuberous sclerosis complex with a high priority, subject to Special Authority criteria to be developed with input from paediatric neurologists.

8.6.1 The Committee made this recommendation based on the high unmet health need for patients with refractory seizures resulting from TSC, particularly young patients, the moderate quality of evidence and moderate evidence of benefit. The Committee considered the clinical effectiveness of mTOR inhibitors in this indication was a class effect and therefore either everolimus or sirolimus could be considered for funding, depending on fiscal risk and commercial arrangements and suitability of formulations.

Discussion

8.7 The Committee considered a request from PHARMAC to consider multiple applications for the use of mTOR inhibitors (everolimus and sirolimus) for the treatment of complications associated with Tuberous Sclerosis Complex (TSC). The Committee noted that in addition to the applications received, PHARMAC requested the Committee particularly consider use of mTOR inhibitors for the treatment of renal angiomyolipoma and refractory seizures associated with TSC, noting there may also be a role for mTOR inhibitors in the treatment of other clinical complications of TSC.

8.8 The Committee noted that PHARMAC has previously considered everolimus and sirolimus for renal angiomyolipoma(s) and refractory seizures associated with TSC through the Named Patient Pharmaceutical Assessment (NPPA) process for a small number of patients.

8.9 The Committee noted that everolimus has FDA approval for use in treatment of subependymal giant cell astrocytoma (SEGA) associated with TSC and other TSC disease, but sirolimus is not approved by the FDA for this indication. Members noted everolimus for use in the treatment of SEGA associated with TSC is Medsafe approved, however approval has not been sought for everolimus in other TSC disease to date and these would be unapproved indications. Sirolimus is not approved for any TSC-related disorder in New Zealand, however the available formulations may make this a reasonable option. Members noted that there is a liquid formulation that would be suitable to use in children (sirolimus 1mg/ml oral solution); everolimus is only available in tablet form. Both everolimus and sirolimus are listed on the Pharmaceutical Schedule for other funded indications. Members noted that treatment is continued indefinitely for these funded indications, if the treatment is effective.

8.10 The Committee noted that TSC is a genetic disorder characterised by the development of benign tumour-like malformations in multiple organ systems; 80% of these mutations occur de novo, with the remainder inherited. The Committee noted that the disease burden increases with age, complications can develop from birth or infancy, and the disease can manifest clinically in the brain, eyes, heart, kidneys, lungs, skin. Disease manifestations can also include impaired cognition, autism, and bipolar disorder. The Committee considered there is a significant unmet health need in patients with TSC but noted that there is minimal quality of life data available for this condition. Members considered that in the later stages of disease, there is increased health need due to respiratory failure.

8.11 The Committee noted that development of renal angiomyolipomas is a common, clinically significant complication in TSC, the prevalence of which increases with age. The Committee noted that renal angiomyolipomas are associated with impaired renal function and also that progressive enlargement is a risk factor for spontaneous retroperitoneal haemorrhage and clinically significant haematuria. The Committee considered that patients with renal angiomyolipomas have a high health need due to impaired renal function and bleeding risk, although it is difficult to predict which patients may experience haemorrhage. Members noted clinical practice and treatment guidelines often consider larger tumours are more likely to bleed, however with limited supporting evidence, it is uncertain if this is the case.

The Committee considered that the families/whānau of patients with renal angiomyolipomas may have additional health needs if a patient's disease results in renal failure.

8.12 The Committee noted that epilepsy is one of the most frequent and significant causes of morbidity in TSC and is often the presenting symptom. The Committee noted that seizures, caused by benign brain lesions known as tubers, are present in 80 to 90% of patients with TSC before the age of 3 years. Seizure types vary, with infantile spasm being most common at diagnosis; however, focal, tonic-clonic and generalised onset seizures can also occur. The Committee considered that patients who have refractory seizures associated with TSC have a high health need due to the significant cognitive effects of the disease, and considered that parents, caregivers and family/whānau of these patients may have a health need due to the impact of this disease in a young patient group. Members considered that about two-thirds of patients with TSC and epilepsy use three or more antiepileptic medications, and about 25% have neurosurgical treatment.

8.13 The Committee noted that there is no data to indicate the Māori are disproportionately affected by TSC.

8.14 The Committee noted that the patient group with non-seizure related complications of TSC is likely relatively small, around 20 patients per year. However, there is uncertainty regarding how many people would experience more than one complication of TSC and require treatment with an mTOR inhibitor. Members noted that PHARMAC staff estimates were based on uptake of everolimus use in Australia for renal angiomyolipoma which would be affected by any funding criterion relating to tumour size.

8.15 The Committee considered that the number of New Zealand patients with refractory seizures related to TSC would be influenced by the number of previous antiepileptic treatments required to be trialled prior to mTOR therapy. Members noted PHARMAC staff estimated this group to be approximately 30 to 40 people per year, however, this would increase if the required number of previous antiepileptic treatments were reduced, or would reduce if there was overlap between the group of people with refractory seizures and those with other clinically significant complications associated with TSC.

Class effect

8.16 The Committee noted there are no head-to-head studies comparing everolimus with sirolimus for TSC, however, the Committee consider it is likely that there is a class effect for these agents, with minimal difference in effect between the two mTOR inhibitors. Members noted that everolimus clinical trial data is more robust and includes three randomised controlled trials, whereas the evidence for sirolimus predominantly consists of case series, cohort studies and small studies.

8.17 The Committee considered that it is likely that the mTOR inhibitors would provide benefit to the main patient subgroups with TSC, in addition to the patient groups who have other complications associated with TSC.

8.18 The Committee considered that there is the potential for long-term adverse events (AEs) resulting from immunosuppression due to mTOR inhibitors and that this would be especially relevant for young patients eg. commencing mTOR inhibitor treatment at 1 year of age or less, due to the risk of developing skin cancers, lymphoma and other types of cancer.

8.19 The Committee noted that the significant cost difference, with everolimus currently being more expensive, and suitability factors, such as availability in a liquid formulation, would be important considerations in funding an mTOR inhibitor for this patient group.

Refractory seizures associated with TSC

8.20 The Committee noted the results from the phase 3, double blind, randomised (1:1:1), placebo-controlled EXIST-3 trial comparing high exposure everolimus (9-15 ng/mL), low exposure everolimus (3-7 ng/mL), with placebo, in 366 patients with TSC and treatment-resistant seizures who were receiving between one and three concomitant antiepileptic drugs (French et al. Lancet. 2016:388;2153-63). The Committee noted that the primary endpoint was the change from baseline in seizure frequency during the 12-week maintenance period, defined as response rate (the proportion of patients achieving ≥50% reduction in seizure frequency) and median percentage reduction in seizure frequency.

8.21 The Committee noted that the response rate in the EXIST-3 trial was 40% with high exposure everolimus (95% CI: 31.5 to 49, P<0.0001), 28.2% with low exposure everolimus (95% CI: 20.3 to 37.3, P=0.0077) and 15.1% with placebo (95% CI: 9.2 to 22.8). The Committee noted that after 18 weeks, the median percentage reduction in seizure frequency was 39.6% with high exposure everolimus (95% CI: 35.0 to 48.7), 29.3% with low dose everolimus (95% CI: 18.8 to 41.9) and 14.9% (95% CI: 0.1 to 21.7) with placebo.

8.22 The Committee noted that grade 3 or 4 adverse events (AEs) were reported in 24%, 18% and 11% of EXIST-3 trial patients who received high exposure, low exposure and placebo, respectively. The Committee noted that serious AEs were reported in 14% of patients in the high exposure group, 14% of patients in the low exposure group and 3% of patients in the placebo group.

8.23 Members noted the results of a post-hoc analysis of about 300 patients from the EXIST-3 trial, including 104 patients less than six years of age and 195 who were six years or older (Curatolo et al. Lancet Child Adolesc Health. 2018;7:495-504). Members noted the response rates in younger patients who received high dose everolimus (59.5%, P=0.0003), low dose everolimus (30.3%, P=0.2245) or placebo (17.6%); and the response rates in older patients who received high dose everolimus (30.0%, P=0.0179), low dose everolimus (27.0%, P=0.0491) or placebo (12.9%). Members considered that the other results reported by the authors, including median reduction in seizure frequency, sustained seizure reduction after 1 year and median percentage reduction in seizure frequency, were very consistent.

8.24 The Committee also noted evidence from a randomised, controlled clinical trial of sirolimus for the treatment of intractable epilepsy in children with TSC (Overwater et al. Neurology. 2016:87;1011-8).

8.25 The Committee noted that a systematic review of mTOR inhibitors suggests that there is a reduction in seizure frequency associated with use of these agents (Li M et al. Orphanet J Rare Dis. 2019;14:39).

8.26 The Committee considered that the use of mTOR inhibitors for the treatment of refractory seizures associated with TSC may result in additional AEs compared to other available treatment options.

8.27 The Committee considered that the use of mTOR inhibitors for the treatment of refractory seizures associated with TSC would be an ongoing, indefinite treatment. The Committee considered that the group of patients with TSC who have treatment-resistant epilepsy and have previously trialled a number of pharmaceutical treatments for epilepsy would be those most likely to receive the greatest benefit from mTOR inhibitors. The Committee considered that the benefit of treatment would be determined through a reduction in seizure frequency eg. 50% reduction from pre-mTOR treatment baseline, and improvement in quality of life of the patient and that of their family/whānau. Members noted some patients may go on to receive surgery, however, shrinking the tumour (with mTOR treatment) prior to surgery would be beneficial.

8.28 The Committee noted that the proposed funding criteria included prior use of six anti-epileptic medications, however, the clinical trial evidence only required a past trial of three medications. The Committee considered that it would require significant time for a trial six

anti-epileptic medications and that this could delay use of, and consequently the benefits from, mTOR inhibitors.

8.29 The Committee considered that specific advice eg. from neurologists may be needed to determine an appropriate number of previous anti-epileptic medications for the initial funding criteria, and to identify appropriate measures and increments of quality of life improvement for inclusion in the renewal criteria. The Committee considered that the evidence did not suggest any difference in clinical benefit according to patient age, therefore there is no rationale to include age in the funding criteria.

Clinically significant complications resulting from TSC (including renal angiomyolipoma)

8.30 The Committee noted evidence from the phase 3, randomised, double-blind, placebo-controlled EXIST-2 trial comparing oral everolimus (10 mg per day) to placebo in 118 adult patients with at least one 3cm or greater angiomyolipoma, with TSC or sporadic lymphangioleiomyomatosis (Bissler et al. Lancet. 2013:381;817-24). The Committee noted that the angiomyolipoma response rate was 42% with everolimus (95% CI: 31-53%) and 0% with placebo (0-9%) after median follow-up of 34 and 38 weeks for placebo and everolimus, respectively. The Committee noted that the most commonly reported AEs were stomatitis, nasopharyngitis and acne-like skin lesions.

8.31 The Committee noted evidence from the long-term, open-label follow-up of 112 patients from the EXIST-2 trial who received everolimus continued at the same dose, or everolimus started at a dose of 10 mg per day in patients who previously received placebo (Bissler et al. Nephrol Dial Transplant. 2016:31;111-9). The Committee noted that after median medication exposure of 28.9 months, the response rate in 107 patients with angiomyolipoma was 54% and that the proportions of patients achieving angiomyolipoma reductions of 30% or greater and 50% or greater increased over time, reaching 81.6% (62/76) and 64.5% (49/76) by week 96. The Committee noted that no renal bleeding events were reported in everolimus-treated patients, no new safety issues were identified, and the long-term safety profile was consistent with previous reports.

8.32 The Committee noted evidence from the four-year, open-label follow-up of 112 patients from the EXIST-2 trial who received everolimus 10 mg per day, or similar tolerated dose, for up to four years (Bissler et al. PLoS One. 2017:12(8): e0180939). The Committee noted that, after median 46.9 months duration of exposure to everolimus, 58% of patients (95% CI: 48.3% - 67.3%) achieved angiomyolipoma response and 14.3% (16) of patients experienced angiomyolipoma progression at some point in the study. The Committee noted that no angiomyolipoma-related bleeding or nephrectomies were reported, and that the most common AEs suspected to be treatment-related were stomatitis (42%), hypercholesterolemia (30.4%), acne (25.9%), aphthous stomatitis and nasopharyngitis (each 21.4%).

8.33 The Committee considered that the evidence from the EXIST-2 trial demonstrated that most patients had achieved responses to everolimus and that these were maintained, although it was unclear whether any reduction conveys clinical benefit or changes renal function. Members considered there is limited evidence that targeting treatment to those with larger angiomyolipoma (greater than 3 or 4 cm) leads to clinically significant outcomes for patients, however this seems likely. Members considered that angiomyolipomas regress in volume during everolimus treatment, but the EXIST-2 trial results suggested that the volume of angiomyolipomas was likely to increase if everolimus is discontinued.

8.34 The Committee noted evidence from the open-label, non-randomised study in 25 adults with TSC or sporadic lymphangioleiomyomatosis who had at least one angiomyolipoma of 1cm in size, who received sirolimus dosing based on target blood levels (1-5 ng/mL) for 24 months to determine whether sirolimus reduces the angiomyolipoma volume (Bissler et al. N Engl J Med. 2008:358;140-51). The Committee noted that the mean angiomyolipoma volume at 12 months was 53.2% (±26.6%) of the baseline value, and at 24 months, five patients had a persistent reduction in volume of 30% or more. The Committee noted that,

at 6 to 12 months after stopping sirolimus, the mean angiomyolipoma volume had increased to 76.8% (±27.5%) of the baseline volume.

8.35 The Committee also noted the following open-label, phase II clinical trial evidence for sirolimus for the treatment of complications (including angiomyolipomas) associated with TSC or sporadic lymphangioleiomyomatosis:

- Davies et al. Clin Cancer Res. 2011:17;4071-81
- Dabora et al. PLoS One. 2011:6(9): e23379

8.36 The Committee considered the quality of evidence for use in angiomyolipoma and other complications is moderate for everolimus and low for sirolimus due to the lack of available studies. The Committee considered that the use of mTOR inhibitors for the treatment of renal angiomyolipoma and other clinically significant complications resulting from TSC would be a long-term treatment and noted that there is no data to support intermittent use at this time. The Committee considered that the benefit of treatment would be determined through clinical and radiological improvements (reduction in tumour size, stabilisation or improvement in organ function) and quality of life improvement.

General

8.37 The Committee considered that cost-effectiveness analysis of mTOR inhibitors for these indications should consider dose adjustments and quality of life improvements.

8.38 The Committee considered that a small number of patients with TSC would be excluded if funding criteria for mTOR inhibitors was targeted to only patients with renal angiomyolipoma(s) or refractory seizures. The Committee considered that this small group of patients, eg. those with lymphangioleiomyomatosis, would be expected to benefit from treatment with an mTOR inhibitor and that funding of treatment for such patients could be considered through the NPPA pathway. However, on balance a pragmatic approach would be to include other complications in the group recommended for funding through the Pharmaceutical Schedule without detailing each potential complication. The Committee considered that PHARMAC staff would need to estimate the maximum population of people with TSC that would be included in this broader definition in order to manage any fiscal risk of proposed patient group.

9 Multiple Sclerosis Treatments, widening access

Application

9.3 The Committee reviewed a funding application for widening access to multiple sclerosis (MS) treatments in three settings:

9.3.1 Removing the gradient stopping criteria such that funding would cease should EDSS score of 4.5 be reached, regardless of the EDSS score at entry.

9.3.2 Amending the entry criteria such that access to funding would be from EDSS 0 – 5.5, with funding ceasing should EDSS 6.0 be reached, regardless of the EDSS score at entry.

9.3.3 Amending the entry criteria to include funding for clinically isolated syndrome (CIS).

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

Recommendation

9.5 The Committee **recommended** amending the entry criteria such that access to funding for MS treatments would be from EDSS 0 to EDSS 5.5, with funding ceasing should an EDSS

of 6.0 be reached, regardless of the EDSS score at entry, with a high priority. This was based on the high health need of people with MS and their carers, the financial impact of widening access, the possible QALY gains from widening access and the practicalities of clinically measuring disease progression.

9.6 The Committee **recommended** the application to widen access to Multiple Sclerosis treatments for the treatment of CIS be declined. This was based on a lack of good quality evidence that earlier treatment, at the stage of CIS, improves long-term health outcomes. However, the Committee noted that it would be happy to review a funding application again in the future that included new evidence (not previously considered) that supports long-term health outcomes from treatment of CIS.

Discussion

Amending EDSS entry and stopping criteria

9.7 The Committee noted that at its November 2018 meeting it had recommended PHARMAC staff conduct analysis to determine what the financial impact would be of amending the stopping criteria of MS treatments to 4.5, 5.5 and 6.0 and bring this back to the Committee for its view. The Committee noted that this has now been completed and PHARMAC was seeking a recommendation from the Committee on this.

9.8 The Committee considered the following previous clinical advice, and funding submissions, that had been provided on the widening access:

- Record of the Neurological Subcommittee September 2013 meeting
- Record of the PTAC February 2014 meeting
- Multiple Sclerosis New Zealand (MSNZ) funding application (June 2017)
- Record of the PTAC November 2017 meeting
- Record of the MSTAC June 2018 meeting (detailed in PTAC 2018 meeting record)
- MSNZ funding application resubmission (June 2018)
- Record of the Neurological Subcommittee July 2018 meeting
- Record of the PTAC November 2018 meeting

9.9 The Committee considered the high health need of people with MS and their carers, and the significant QOL loss associated with disease progression.

9.10 The Committee considered an observational, open label, prospective study regarding long-term safety of natalizumab and its impact on annualised release rate and EDSS progression in patients with RRMS (Butzkueven et al. J Neurol Neurosurg Psych. 2014;85:1190-7). The Committee noted that this was a 5-year interim analysis, where 4821 patients were originally enrolled, and that follow-up was for at least 4 years from natalizumab commencement in 468 patients and at least 2 years in 2496 patients. The Committee noted that the authors reported the mean annualised relapse rate decreasing from 1.99 in the 12 months prior to baseline to 0.31 on natalizumab therapy ($p<0.0001$) and remaining low after 5 years. The Committee noted that the authors reported the mean EDSS scores remaining unchanged up to 5 years for those who were still in the study at follow-up. However, the Committee considered that the study had significant limitations due to the low proportion of participants that completed the follow-up, and that the results were likely representative of only the subset those that did well/responded to treatment with natalizumab.

9.11 In addition the Committee considered two publications (Wiendl et al. PLoS One. 2016;11:1-14; Trojano et al. Mult Scler Relat Disord. 2018;24:11-19) presenting further analyses from the Butzkueven et al observational study (paragraph 14.9). The Committee considered that the limitations of these studies were the same as the parent study: again, that the results were likely representative of only the subset of those that do well/respond to treatment with natalizumab.

9.12 The Committee considered budget impact analysis conducted by PHARMAC staff.

9.12.1 The Committee noted that PHARMAC staff had undertaken budget impact analysis for EDSS 0-4.5 and EDSS 0-6.0 only. The Committee noted that this was because PHARMAC staff considered that the analysis for EDSS 0 – 5.5 was unlikely to significantly differ from EDSS 0 – 6.0, because of the small increment of score change involving a few patients between EDSS 5.5 and 6.0, and that transition probabilities for half states of disease have not been previously reviewed by PTAC.

9.12.2 The Committee noted that as each of the MS treatments have different net prices and different proportionate market shares, and that for this reason PHARMAC staff had used an average drug price to estimate the budget impact of amending the entry and stopping criteria.

9.12.3 The Committee noted that PHARMAC staff estimated the additional cost to the combined pharmaceutical budget of expanding access to EDSS 4.5 would be **[Withheld].**

9.12.4 The Committee noted that PHARMAC staff estimated the additional cost to the combined pharmaceutical budget of expanding access to EDSS 6.0 would be **[Withheld].**

9.13 The Committee noted that when it had first reviewed funding applications for the new Multiple Sclerosis treatments they were very expensive treatments, but that over time the prices for some of these had significantly decreased, due to various PHARMAC commercial arrangements.

9.14 The Committee considered cost effectiveness analysis conducted by PHARMAC staff.

9.14.1 The Committee noted that PHARMAC staff had estimated the cost effectiveness of expanding access to all MS treatments gaining between **[Withheld]** per $1 million (widening access up to EDSS 6.0).

9.14.2 The Committee noted that these estimates (paragraph 14.13.1) assumed that the treatments would continue to provide a similar health benefit (in terms of relative risks of disease progression) at higher EDSS states as occurs in lower EDSS states, as modelled previously. The Committee noted that the economic modelling also assumed that the treatment effect on disease progression would remain the same irrespective of how many lines of treatment a patient had trialled. The Committee considered however that it was more likely that effects on disease progression diminish with each line of treatment.

9.14.3 The Committee noted that drug costs, relative risks of disease progression and administration costs were the average of the following treatments: natalizumab, fingolimod, dimethyl fumarate, and ocrelizumab.

9.14.4 The Committee considered that economic modelling for MS treatments was highly complex, because of the multiple disease states that patients progress through and the associated with the variable time course of progression of individual patients with MS.

9.15 The Committee considered that it had not seen robust evidence demonstrating MS treatments having similar efficacy at higher EDSS states (up to 6.0); however in the absence of evidence, and due to the complexity of modelling the disease, it accepted the simplified approach of modelling similar heath gains at EDSS states of 4.5-6.0, with the caution this may overestimate the true QALY gains. In addition, the Committee considered the QALY gains would likely be further overestimated due to the assumption that the treatment effects on disease progression would remain the same irrespective of the lines

of treatment that had been trialled; however the Committee acknowledged the complexities of modelling more than two lines of treatment, and accepted this simplified approach too.

9.16 The Committee noted that if a patient was unable to walk 100 meters without aid that would mean an EDSS score of 6.0; and, considered that this was a simple, practical and replicable threshold with which to align stopping criteria.

Clinically isolated syndrome

9.17 The Committee noted that MSNZ had written to PHARMAC requesting that PTAC review its [June 2018] submission in its entirety. The Committee noted that at its November 2018 meeting it had considered in detail both the Neurological Subcommittee and the MSTAC minutes relating to CIS (and MSNZ's applications), amongst other issues. The Committee noted that with regards to CIS, it had considered that the revised McDonald criteria allow for earlier diagnosis of Clinically Definite Multiple Sclerosis (CDMS) but that it had not seen good quality evidence that earlier treatment, at the stage of CIS, improves long-term health outcomes, and that it had not supported a positive recommendation to fund treatments for CIS.

9.18 The Committee considered that it had carefully considered all the information provided by MSNZ, including the original 2017 submission and the 2018 resubmission.

9.19 The Committee considered that there was no new evidence provided to change its original view. The Committee reiterated its previous recommendation that it had not seen good quality evidence that earlier treatment, at the stage of CIS, improves long-term health outcomes, and the Committee therefore determined that the recommendation for funding of treatment for CIS remain a decline. The Committee reiterated that it would be happy to review a funding application in the future that included new evidence (not previously considered) that supports long-term health outcomes from treatment of CIS.

10 Cladribine for the treatment of relapsing-remitting multiple sclerosis

Application

10.3 The Committee reviewed a resubmission from Merck Serono for funding of cladribine in the treatment of relapsing-remitting multiple sclerosis (RRMS).

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

Recommendation

10.5 The Committee **recommended** that, cladribine should be funded only if cost neutral to fingolimod, taking into account that 20% of patients may require redosing with cladribine at 2 years, and the remaining 80% would likely require redosing at 4 years. This recommendation was based on the evidence for efficacy of cladribine, fingolimod being the most likely comparator, and expert opinions regarding retreatment rates.

Discussion

10.6 The Committee considered a resubmission from Merck Serono for the use of cladribine (Mavenclad) for the treatment of RRMS. The Committee noted that the application was originally submitted in May 2018 and was considered by the Neurological Subcommittee in July 2019.

10.7 The Committee noted that the Neurological Subcommittee had recommended that the application be declined, primarily due to uncertainty regarding treatment sequencing following cladribine therapy. PTAC noted that the supplier had now provided a resubmission responding to the points raised by the Neurological Subcommittee.

10.8 The Committee noted that cladribine is now registered with Medsafe for the treatment of RRMS

10.9 The Committee considered that cladribine had a different mechanism of action from other funded treatments for Multiple Sclerosis (MS). The Committee noted that the mechanism of action involved a selective and transient reduction in lymphocytes; with a gradual repopulation over 4-years. The Subcommittee considered that this mechanism of action is different to that of fingolimod, which also has the effect of decreasing lymphocyte counts.

10.10 The Committee considered the 96-week, double-blind, placebo-controlled, phase 3 CLARITY trial (Giovannoni et al. N Engl J Med. 2010;362:416-26) and the 2-year CLARITY extension (CLARITY EXT) trial (Giovannoni et al. Mult Scler. 2018;24:1594-1604), which investigated the efficacy and safety of cladribine in patients with relapsing-remitting multiple sclerosis (RRMS).

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

10.12 The Committee noted that of the 1,184 patients who completed CLARITY, 867 were enrolled in the extension, and that there was a duration of gap between CLARITY and CLARITY EXTENSION. The Committee noted that the gap period was distributed across the treatment groups: the median duration was 40.3 weeks and the maximum duration was between 111 weeks and 118 weeks across the groups (range 0.1-118.0 weeks across all groups). The Committee noted that overall, 10.7% of patients experienced a gap duration of $\leqslant$4 weeks; 44.8% experienced a gap >4 to $\leqslant$43 weeks, and 44.5% had a gap >43 weeks.

10.13 The Committee noted the annualised relapse rate (ARR) in patients treated with cladribine 3.5 mg/kg in CLARITY followed by placebo in CLARITY EXTENSION was not significantly different from that in patients who received cladribine 3.5 mg/kg in both CLARITY and CLARITY EXTENSION (0.15 [0.09, 0.21] v 0.10 [0.06, 0.13], p=0.06), and that both groups showed comparable proportions of relapse-free patients (75.6% and 81.2%, respectively, p = 0.28). The Committee considered that it was possible that the longer the duration of treatment gap the less the effectiveness of treatment, but further analysis was needed to confirm this.

10.14 The Committee considered safety data from an integrated analysis of clinical trials and follow up in patients with MS regarding the safety profile of cladribine tablets (Comi et al. Mult Scler. 2018;24:1594-1604). The Committee noted the overall adjusted treatment-emergent adverse event (Adj-AE) incidence per 100 patient years (Adj-AE/100PY) in the integrated analysis was 103.29 for patients who received cladribine monotherapy compared with 94.26 for patients who received placebo. The rate of serious TEAEs was reported as 3.57 Adj-AE/100 PY compared with 4.00 Adj-AE/100 PY for patients who received cladribine and placebo, respectively. Lymphopenia and herpes zoster were more common in patients receiving cladribine; however, there were no cases of systemic, serious disseminated herpes zoster attributed to treatment with cladribine tablets. The Committee noted that one patient had been reported to have experienced re-activation of tuberculosis and died. The Committee noted that the authors had reported that there was no increase in malignancy rates with cladribine relative to placebo.

10.15 The Committee noted that currently there are no head-to-head trials comparing cladribine to a relevant comparator. The Committee considered, based on indirect analysis (Giovannoni G. Curr Opin Neurol. 2018;31:233-43, Siddiqui et al. Curr Med Res Opin. 2018;34:1361-71 and Berardi et al. Curr Med Res Opin. 2019;35:1371-8), that cladribine is likely to have similar efficacy to fingolimod.

10.16 The Committee noted that the Neurological Subcommittee had considered that there was a lack of evidence regarding treatment sequencing following cladribine treatment and that it was unclear how patients who exhibit no progression at four years should be treated subsequently, or how patients who relapsed during the treatment period should then be treated.

10.17 The Committee noted that there is currently no data on treatment sequencing and retreatment. The Committee considered the following summarised expert opinions (provided by a Merck Serono Multiple Sclerosis Advisory Board):

10.17.1 That if cladribine was effective during years 3 and 4, clinicians would be likely to treat again with cladribine rather than to switch therapy; and that less than 20% would require retreatment in years 3 and 4, based either on clinical evidence of relapse or reactivation of disease.

10.17.2 That if there was evidence of disease activity before the end of year 2, a decision to switch or retreat would depend on the clinical situation of the individual patient.

10.18 The Committee considered that the above estimates of treatment sequencing and retreatment (paragraphs 15.16.1, and 15.16.2), seemed reasonable.

10.19 The Committee noted that the Neurological Subcommittee had considered that pre-treatment with cladribine might increase the risk of progressive multifocal leukoencephalopathy (PML) on subsequent treatment with natalizumab. The Committee noted that the Medsafe data sheet for cladribine provided the following relevant information "In the clinical trial data base of cladribine in MS (1,976 patients, 8,650 patient years) no case of PML has been reported. However, an MRI should be considered before initiating Mavenclad (usually within 3 months). This is particularly recommended if patients are switched from other MS agents that have a risk of PML."

10.20 The Committee noted that the Supplier had provided the following view in its resubmission regarding pregnancy and cladribine:

10.20.1 That cladribine would be an appropriate high efficacy option for women considering a pregnancy following treatment with cladribine tablets, and that that a pregnancy can start 6 months after the last dose of cladribine tablets in Year 2. Since no further treatment is required in Years 3 and 4, this provides a window of opportunity for pregnancy and breast feeding.

10.21 The Committee noted the Supplier's view regarding pregnancy and cladribine. However, it also noted that cladribine is classified by the Australian Therapeutic Goods Administration as Category D in pregnancy and considered that it is therefore unlikely to be an appropriate treatment option for women planning pregnancy.

10.22 The Committee noted that the Neurological Subcommittee considered that if cladribine was listed, approximately 25% of patients receiving fingolimod and dimethyl fumarate may switch due to the convenience associated with administration; however, the majority of patients who would receive cladribine would be treatment-naïve. The Committee noted the Supplier had provided PHARMAC with data from its Australian market access programme, in which 23% of those who received cladribine were treatment-naïve.

10.23 The Committee considered that monitoring while on treatment with cladribine included lymphocyte counts and MRI scans in year 3 and 4.

10.24 The Committee recommended that cladribine should be funded only if cost neutral to fingolimod, taking into account that 20% of patients may require redosing with cladribine at 2 years, and the remaining 80% would likely require redosing at 4 years. This

recommendation was based on the evidence for efficacy of cladribine, fingolimod being the most likely comparator, and expert opinions regarding retreatment rates.

11 Adalimumab and etanercept for juvenile idiopathic arthritis – widening of access

Application

11.3 The Committee reviewed the clinician application for widening of access to adalimumab and etanercept for juvenile idiopathic arthritis.

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

Recommendation

11.5 The Committee recommended that the funding of adalimumab and etanercept for the treatment of patients with juvenile idiopathic arthritis (JIA) be widened with a high priority, subject to the following Special Authority criteria (additions in bold and deletions in strike through):

ADALIMUMAB
Initiation – juvenile idiopathic arthritis
Rheumatologist or named specialist
Re-assessment required after 6 months
Either:
1 Both:
- 1.1 The patient has had an initial Special Authority approval for etanercept for juvenile idiopathic arthritis (JIA); and
- 1.2 Either:
  - 1.2.1 The patient has experienced intolerable side effects from etanercept; or
  - 1.2.2 The patient has received insufficient benefit from etanercept to meet the renewal criteria for etanercept for JIA; or

2 All of the following:
- 2.1 Patient diagnosed with Juvenile Idiopathic Arthritis (JIA); and
- 2.2 To be used as an adjunct to methotrexate therapy or monotherapy where use of methotrexate is limited by toxicity or intolerance; and
- 2.3 Either:
  - 2.3.1 Patient has polyarticular course JIA for 6 months duration or longer; and
    - 2.3.1.1 Either:
      - 2.3.1.1.1 At least 5 swollen joints and at least 3 joints with limitation of motion, pain and tenderness; or
      - 2.3.1.1.2 Moderate or high disease activity (cJADAS score of at least 2.5) after a 3-month trial of methotrexate (at a dose of 10-20 mg/m^2 weekly or at the maximum tolerated dose); or
      - 2.3.1.1.3 Low disease activity (cJADAS score between 1.1 and 2.5) after a 6-month trial of methotrexate; and
    - 2.3.1.2 Patient has tried and not responded to a therapeutic trial of oral corticosteroids (prednisone 0.25 mg/kg or at the maximum tolerated dose); or
  - 2.3.2 Patient has oligoarticular course JIA for 6 months duration or longer; and
    - 2.3.2.1 Either:
      - 2.3.2.1.1 At least 2 active joints with swelling or limited range of motion; or
      - 2.3.2.1.2 Moderate or high disease activity (cJADAS score greater than 1.5) with poor prognostic features after a 3-month trial of methotrexate (at a dose of 10-20 mg/m^2 weekly or at the maximum tolerated dose); or
      - 2.3.2.1.3 High disease activity (cJADAS score greater than 4) after a 6-month trial of methotrexate.

ETANERCEPT
Restricted
Initiation – juvenile idiopathic arthritis
Rheumatologist or named specialist
Re-assessment required after 6 months
Either:
1 Both:
- 1.1 The patient has had an initial Special Authority approval for adalimumab for juvenile idiopathic arthritis (JIA); and

1.2 Either:
1.2.1 The patient has experienced intolerable side effects from adalimumab; or
1.2.2 The patient has received insufficient benefit from adalimumab to meet the renewal criteria for adalimumab for JIA; or

2 All of the following:
2.1 Patient diagnosed with Juvenile Idiopathic Arthritis (JIA); and
2.2 To be used as an adjunct to methotrexate therapy or monotherapy where use of methotrexate is limited by toxicity or intolerance; and
2.3 Either:
2.3.1 Patient has polyarticular course JIA for 6 months duration or longer; and
2.3.1.1 Either:
2.3.1.1.1 At least 5 swollen joints and at least 3 joints with limitation of motion, pain and tenderness; or
2.3.1.1.2 Moderate or high disease activity (cJADAS score of at least 2.5) after a 3-month trial of methotrexate (at a dose of 10-20 mg/m^2 weekly or at the maximum tolerated dose); or
2.3.1.1.3 Low disease activity (cJADAS score between 1.1 and 2.5) after a 6-month trial of methotrexate; and
2.3.1.2 Patient has tried and not responded to a therapeutic trial of oral corticosteroids (prednisone 0.25 mg/kg or at the maximum tolerated dose); or
2.3.2 Patient has oligoarticular course JIA for 6 months duration or longer; and
2.3.2.1 Either:
2.3.2.1.1 At least 2 active joints with swelling or limited range of motion; or
2.3.2.1.2 Moderate or high disease activity (cJADAS score greater than 1.5) with poor prognostic features after a 3-month trial of methotrexate (at a dose of 10-20 mg/m^2 weekly or at the maximum tolerated dose); or
2.3.2.1.3 High disease activity (cJADAS score greater than 4) after a 6-month trial of methotrexate.

[ADALIMUMAB/ETANERCEPT]
Continuation – juvenile idiopathic arthritis
Rheumatologist or named specialist, or on the recommendation of a rheumatologist or named specialist
Re-assessment required after 6 months
Both:
1 Treatment is to be used as an adjunct to methotrexate therapy or monotherapy where use of methotrexate is limited by toxicity or intolerance; and
2 Either:
2.1 Following 3 to 4 months' initial treatment, the patient has at least a 50% decrease in active joint count and an improvement in physician's global assessment from baseline; or
2.2 On subsequent reapplications, the patient demonstrates at least a continuing 30% improvement in active joint count and continued improvement in physician's global assessment from baseline.

11.6 The Committee made this recommendation based on the health need of patients with JIA with severe pain and joint involvement, and evidence for a prolonged treatment benefit resulting in long-term remission. The Committee considered that this recommendation and the proposed changes to the Special Authority criteria would widen access to these treatments for patients with eoJIA, PsA and ERA.

11.7 The Committee noted that the Special Authority criteria for tocilizumab also refers to numbers of joints and considered that, if wider access for adalimumab and etanercept is funded, the tocilizumab Special Authority criteria should be reviewed.

11.8 The Committee considered that the Rheumatology Subcommittee could provide advice regarding the appropriate response assessment outcomes eg. ACR Pedi 30 in combination with clinical Juvenile Arthritis Disease Activity Score (cJADAS), for use in cost-effectiveness modelling and advice regarding whether there is a need for stopping criteria.

Discussion

11.9 The Committee noted that Juvenile Idiopathic Arthritis (JIA), formerly called Juvenile Rheumatoid Arthritis (JRA), is a chronic inflammatory condition of unknown cause that affects the joints, commences prior to the age of 16, persists for at least 6 weeks, and is diagnosed clinically (supported by ultrasound or MRI findings). The Committee noted that JIA can have an oligoarticular course, which affects 4 or fewer joints at any time, or polyarticular course, which affects 5 or more joints at any time.

11.10 The Committee noted that the International League of Associations for Rheumatology (ILAR) classification system delineates cases into mutually-exclusive categories of JIA based on predominant clinical and laboratory features (Petty et al. J Rheumatol. 2004;31:390-2). The Committee noted that the applicant requested funding for patients with any of the following ILAR subtypes:

- Extended oligoarticular (eoJIA), where 1-4 joints are involved during the first 6 months of illness and more than 4 joints affected after the first 6 months; and
- Juvenile psoriatic (PsA), where children have arthritis and psoriasis, or arthritis and at least two other specific features (eg dactylitis, psoriasis in a relative); and
- Enthesitis-related arthritis (ERA), where children have arthritis and enthesitis, or arthritis or enthesitis with two other specific factors (eg sacroiliac joint tenderness, presence of specific antigen).

11.11 The Committee considered that patients with JIA (especially eoJIA or other oligoarticular course types) have a high health need due to substantial pain from disease involvement in even a few joints, based on joint count and physician-assessed pain scores. Members considered that JIA seriously impacts on the health of families/whānau of patients with JIA. Members considered that, based on anecdotal evidence for health disparities in patients with JIA, the disease could disproportionately affect Māori, Pacific people or other patient groups if other factors that result in reduced engagement with the health system are present.

11.12 The Committee noted the applicant's new patient case estimates of approximately 45 JIA cases nationally per year (21 oligoarticular course, 11 polyarticular course, 7 ERA, 4 systemic JIA and 2 PsA). The Committee considered that the application represents the views and expertise of the four paediatric rheumatologists who provide expert advice regarding treatment of New Zealand children with JIA and who would provide reasonable estimates of suitable patient numbers. The Committee considered that, when compared to the applicant's estimates, PHARMAC staff's prevalence-based estimate of 90 per year are high. The Committee noted that there would be a natural departure of patients from the JIA patient population into the adult population.

11.13 The Committee noted that the tumour necrosis factor (TNF) inhibitors adalimumab and etanercept are funded for the treatment of JIA, limited to patients with either: intolerable side effects from, or insufficient benefit from, the alternate agent (adalimumab or etanercept); and for patients with severe active polyarticular course JIA for at least 6 months, with persistent symptoms of poorly-controlled and active disease, who meet other criteria including trials of other therapies and use with methotrexate (if appropriate).

11.14 The Committee noted that tocilizumab is funded for the treatment of polyarticular JIA, limited to patients with either: intolerable side effects from, or insufficient benefit from, both adalimumab and etanercept; or for patients with severe active polyarticular course JIA for at least 6 months, with persistent symptoms of poorly-controlled and active disease, who meet other criteria including trials of other therapies, use with methotrexate (if appropriate) and contraindication to TNF inhibitor treatment. Members considered that the number of patients suitable for funded tocilizumab may be useful for reference.

11.15 The Committee noted that adalimumab is Medsafe-approved for use in polyarticular JIA and ERA, and that etanercept is Medsafe-approved for use in eoJIA, ERA, PsA and polyarthritis: at least 5 joints involved during the first 6 months of illness. The Committee noted that there is substantial international and national experience with these agents for the treatment of children with JIA or other diseases, and had no concerns regarding their use in the requested patient populations from the perspective of use outside the specific Medsafe-approved JIA indications, under appropriate specialist supervision.

11.16 The Committee noted that the Juvenile Arthritis Disease Activity Score (JADAS) is a composite JIA disease activity score based on 4 measures (physician's global assessment

of disease activity, parent/guardian's global assessment of overall wellbeing, number of active joints, and erythrocyte sedimentation rate [ESR]). The Committee noted variants include JADAS-CRP which uses C-reactive protein (CRP) instead of ESR, and cJADAS, a clinical, 3-item version of JADAS that excludes both ESR and CRP. The Committee noted that the applicant stated the cJADAS score was a validated measure based on the 2013 update of 2011 American College of Rheumatology (ACR) recommendations. It is an easily applied surrogate measure of disease activity in clinical practice.

11.17 The Committee noted that the American College of Rheumatology (ACR) Paediatric (Pedi) 30 treatment response is used in JIA, defined as at least a 30% improvement from baseline in three of six variables, with no more than one other variable worsening by >30 %. The Committee noted that the ACR Pedi 50, 70, 90 and 100 require the corresponding percentage improvement in at least three variables. The Committee considered that, although this measure is used in clinical trials, its application in a clinical setting is significantly more cumbersome than that of cJADAS.

11.18 The Committee noted that the evidence for etanercept in patients with eoJIA, ERA and PsA comes from the phase IIIb, open-label, prospective, multicentre, CLIPPER study, which included 127 children with eoJIA, ERA or PsA who received etanercept 0.8 mg/kg once weekly (maximum 50 mg) for 12 weeks and were followed-up for 96 weeks (Horneff et al. Ann Rheum Dis. 2014;73:1114-22; Constantin et al. J Rheumatol. 2016;43:816-24).

11.18.1 The Committee noted that CLIPPER used historical placebo controls as comparison, and that the patients enrolled had less severe disease than patients who would access funded etanercept according to the current Special Authority criteria.

11.18.2 The Committee noted that at 12 weeks ACR 30 responses were achieved in 88.6% of CLIPPER patients overall (95% CI: 81.6% to 93.6%) with similar results in the eoJIA, PsA and ERA subgroups, and that at 96 weeks ACR 30 responses were achieved in 84.3% of patients overall (95% CI: 76.7% to 90.1%). The Subcommittee noted that the results signalled a benefit when compared to a historical placebo, and less benefit (although still an effect) when compared to a historical active control.

11.18.3 The Committee considered that short-term safety reported in CLIPPER was acceptable.

11.18.4 The Committee noted that about 10% of patients with eoJIA had inactive disease at the end of the CLIPPER trial, and other evidence suggested prolonged remission in patients with JIA (Minden et al. Arthritis Care Res (Hoboken). 2019;71:471-81). Members considered that this suggested the potential of a 'window of opportunity', whereby disease course could be radically improved or even cured.

11.19 The Committee noted the results of CLIPPER-2, an extension of the CLIPPER study, which reported data from a total of 6 years trial participation in 109 CLIPPER participants (Foeldvari et al. Arthritis Res Ther. 2019;21:125). The Committee noted that 24% of patients had JADAS inactive disease at 6 years. The Committee considered that these results suggest patients with early response at 12 weeks maintained this improvement long-term. The Committee noted that frequently reported treatment-emergent adverse events included headache, arthralgia, pyrexia, diarrhoea and leukopenia. Although there were no reported deaths there was one report of malignancy, a patient with non-Hodgkin lymphoma.

11.20 The Committee noted evidence from an industry-funded 'BIKER' registry, which prospectively collected data over 11 years for 1,678 patients who received treatment with etanercept for JIA, including eoJIA, ERA and PsA (Windschall et al. Clin Rheumatol. 2015;34:61-9). The Committee considered that the BIKER registry patient population was similar to the patient population requested by the applicant, and noted that BIKER patients

had 4.3 affected joints on average and most had previously received methotrexate and non-steroidal anti-inflammatory drugs. The Committee noted that a reduction in JADAS score was reported at 24 months and considered that this was clinically relevant based on anecdotal expert advice.

11.21 The Committee noted the following evidence from randomised trials and prospective observational registry studies that either reported outcomes for the broader JIA groups (polyarticular course JIA and oligoarticular course JIA), or outcomes according to older definitions such as juvenile rheumatoid arthritis (JRA) in patients who received adalimumab or etanercept:

- Windschall et al . Clin Rheumatol. 2016:35;2925-32
- Alexeeva et al. Pediatr Rheumatol Online J. 2017:15;51
- Anink et al. Rheumatology (Oxford). 2013:52;712-7)
- Lovell et al. N Engl J Med. 2000:342;763-9
- Lovell et al. Arthritis Rheum. 2003:48;218-26
- Lovell et al. Arthritis Rheum. 2006:54;1987-94
- Lovell et al. N Eng J Med. 2008:359;810-20

11.21.1 The Committee considered that some evidence supported the safety of etanercept and of adalimumab in these settings and suggests a benefit from early treatment especially in younger children and those with eoJIA. The Committee considered that the four publications by Lovell et al. were of limited value due to different dosing and outcomes and trial design limited to assessing relapses only. The Committed noted the majority of the evidence available was for etanercept, as opposed to adalimumab.

11.22 The Committee noted the following published recommendations:

- Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis: Technology appraisal guidance TA373 [Internet]. National Institute for Health and Care Excellence (UK); Dec 2015 [revised Dec 2018; cited Nov 2019].
- The 2013 update of 2011 American College of Rheumatology recommendations (Ringold et al. Arthritis Rheum. 2013:65;2499-512).

11.23 The Committee noted that the evidence generally uses ACR Pedi scores, however, New Zealand clinicians prefer to use the cJADAS score. Members considered that there are published minimal clinically important difference (MCID) scores for the cJADAS, which vary according to disease severity, based on the BIKER registry.

11.24 The Committee considered that the evidence suggests patients with persistent eoJIA receive the most benefit from treatment commenced for oligoarticular course JIA, however, all children with JIA who meet the criteria to commence on adalimumab or etanercept earlier would benefit from reduced joint damage and pain and from achieving remission. The Committee considered that there are a variety of guidelines regarding the use of TNF inhibitors for JIA, including the recommendation to use one of these agents in cases with axial disease (although this was not specifically requested by the applicant). The Committee noted that TNF inhibitors are not recommended for first-line treatment of JIA.

11.25 The Committee considered that there are long-term risks with the use of etanercept and adalimumab, such as increased risk of malignancy. Members considered that there are now fewer signals of cancer incidence being reported from biologic/disease registries than were previously reported in patients who commenced long-term treatment with disease-modifying anti-rheumatic drugs (DMARDs). Members considered that this may be due to earlier control of inflammation from earlier use of DMARDs. Members noted that previously,

many of the patients in these cancer registries would have had exposure to multiple older systemic DMARDS.

11.26 The Committee considered that widening access to adalimumab and etanercept for JIA could increase the workload of paediatric rheumatologists due to earlier treatment of these patients. The Committee considered that, as these same specialists were the applicants, this workload could be managed adequately by staff and health system resources.

11.27 The Committee considered that the target patient population would be patients with JIA who have trialled some, but not necessarily all, DMARDs, and that some patients would use methotrexate in combination with adalimumab or etanercept, while other patients may be intolerant to methotrexate and therefore use adalimumab or etanercept instead. Members considered that patients may swap between adalimumab and etanercept, but this would be patient-dependent.

11.28 The Committee considered that the response outcome for use in modelling could be the ACR Pedi 30 in combination with the cJADAS score. The Committee considered that the Rheumatology Subcommittee could provide advice regarding appropriate outcomes for PHARMAC to model.

11.29 The Committee considered it likely that widening access to adalimumab and etanercept for JIA would benefit family and whānau through increased periods of remission for the patient, resulting in reduced caregiver stress and consequent health decrements.

11.30 The Committee considered that the Special Authority criteria for adalimumab and etanercept for patients with eoJIA, PsA and ERA should be amended to widen access, with specific changes to the number of affected joints and definitions of disease severity.

11.30.1 The Committee considered it was not appropriate to include a requirement for intra-articular steroid injections in oligoarticular course JIA, noting that such injections frequently need to be given under short general anaesthesia for these children, and rather considered that injections should be performed according to clinical judgment and need.

11.30.2 Members similarly considered that a requirement for patients to have trialled all DMARDs prior to use of adalimumab or etanercept may not be appropriate, as this would take a long period of time, minimising the potential 'window of opportunity' effect.

11.30.3 The Committee considered that it was not appropriate to include the applicant-proposed additional prescribing option of 'according to District Health Board (DHB) protocol', understanding that paediatric rheumatologists would accept non-inclusion. The Committee noted that the proposed SA criteria included prescribing by, or on the recommendation of, a rheumatologist or named specialist, to ensure appropriate prescribing and minimise the risk of slippage.

11.30.4 The Committee noted that currently there are no clear stopping criteria, nor had any been proposed by the applicant, for adalimumab and etanercept for JIA, and considered that this presented a fiscal, and potentially clinical, risk. The Committee suggested that PHARMAC could contact the New Zealand paediatric rheumatologists to ascertain whether stopping criteria would be appropriate, and if so, what these criteria should be.

11.31 The Committee noted that the Special Authority criteria for tocilizumab for JIA also refer to numbers of joints and considered that, if adalimumab and etanercept funding was widened for JIA, the tocilizumab Special Authority criteria should be reviewed and amended if required, for funded consistency between TNF inhibitors.

12 Adalimumab for the first-line biologic treatment of moderate to severely active ulcerative colitis

Application

12.3 The Committee reviewed infliximab usage data provided by PHARMAC and noted the August 2013 and February 2017 applications from AbbVie for adalimumab for the treatment of moderate to severely active ulcerative colitis (UC).

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

Recommendation

12.5 The Committee **recommended** that adalimumab for the first-line biologic treatment of moderate to severely active ulcerative colitis (UC) be funded with a low priority subject to the following Special Authority criteria:

ADALIMUMAB
Initial application – (moderate to severely active ulcerative colitis; first biologic line)
Only from a gastroenterologist. Approvals valid for 3 months for applications meeting the following criteria:
All of the following:

1. Patient has histologically confirmed ulcerative colitis that is moderate to severely active; and
2. Patient is 18 years or older and the Simple Clinical Colitis Activity Index (SCCAI) score is greater than or equal to 4; 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 for an adequate duration (unless contraindicated) and systemic corticosteroids; and
4. Surgery (or further surgery) is considered to be clinically inappropriate.

ADALIMUMAB
Renewal – (moderate to severely active ulcerative colitis; first biologic line)
Only from a gastroenterologist or Practitioner on the recommendation of a gastroenterologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1. Patient is continuing to maintain remission and the benefit of continuing adalimumab outweighs the risks; and
2. Patient is 18 years or older and the SCCAI score has reduced by 2 points or more from the SCCAI score when the patient was initiated on adalimumab; and
3. Adalimumab to be administered at doses no greater than 40 mg every 14 days.

12.6 The Committee made this recommendation based on the high health need of patients with moderate to severely active UC, balanced against the absence of evidence for superiority of adalimumab over infliximab in the first-line biologic treatment of UC, and uncertainty regarding barriers to infliximab use in District Health Boards (DHBs). The Committee noted that DHB infusion resources are under pressure and considered that this factor may contribute to access inequities.

Background

12.7 The Committee noted the history of the supplier's original application for adalimumab for the treatment of moderate to severely active UC that was received in September 2013:

12.7.1 In November 2013, PTAC reviewed the application and recommended it for decline because of limited evidence for sustained clinical effectiveness, lack of long term safety data and high financial risk. PTAC requested further advice from the Gastrointestinal Subcommittee regarding a scoring scale for disease severity.

12.7.2 In May 2014, the application was reviewed by the Gastrointestinal Subcommittee, which agreed with PTAC's recommendation that the application be declined because of limited evidence for sustained clinical effectiveness, as well as a lack of long term safety data and high financial risk. The

Gastrointestinal Subcommittee considered the additional information provided by the supplier was not sufficient to alter this recommendation.

12.7.3 In November 2014, PTAC noted and accepted the Minutes of the Gastrointestinal Subcommittee meeting held on 21 May 2014.

12.8 The Committee noted the history of the supplier's resubmission for adalimumab for the treatment of moderate to severely active UC that was received in February 2017:

12.8.1 In March 2017, the resubmission was reviewed by the Gastrointestinal Subcommittee, which recommended that adalimumab for the first-line biologic treatment of moderate to severely active ulcerative colitis be declined. The Gastrointestinal Subcommittee noted that the efficacy of adalimumab and infliximab had not been directly compared, and considered adalimumab was unlikely to be more efficacious than infliximab.

12.8.2 In November 2017, PTAC reviewed the application for adalimumab for the first-line biologic treatment of moderate to severely active ulcerative colitis and made no formal recommendation. PTAC considered that this is a large patient group and potentially high budget risk, and PTAC requested to review the evidence for the Subcommittee's recommendation.

12.8.3 In May 2018, PTAC reviewed the application for adalimumab for the first-line biologic treatment of moderate to severely active ulcerative colitis and considered that the evidence shows that infliximab is likely to provide better health outcomes than adalimumab when used as a first-line biologic agent to treat ulcerative colitis. PTAC recommended that the application for adalimumab as a first biologic line treatment of ulcerative colitis be deferred until PHARMAC staff report back to PTAC on the availability of infliximab in each DHB.

Discussion

12.9 The Committee noted that the proposal is for the first-line biologic treatment with adalimumab for patients with moderate to severe ulcerative colitis (UC) who are refractory to and/or intolerant to prior systemic therapy, including a stable course of oral corticosteroids.

12.10 The Committee noted that adalimumab is proposed to be administered as a subcutaneous injection with an induction regimen of 160 mg initially then 80 mg at week 2, with subsequent administration at a dose of 40 mg every fortnight subject to sufficient response (determined by a decrease in Simple Crohn's Colitis Activity Index [SCCAI] score of greater than or equal to 2 from initial assessment).

12.11 The Committee noted that the SCCAI is a sum of scores from five questions assessed clinically, and that the Mayo score is a clinically useful but not specifically validated indicator of disease activity that uses clinical and endoscopic parameters. The Committee considered that the SCCAI is a validated, appropriate tool and noted that it is currently used in the Special Authority criteria for infliximab for severe UC.

12.12 The Committee noted that the supplier had proposed for adalimumab to be added as a later line of therapy in patients with moderate UC who have not responded to previous treatment with 5-ASAs, corticosteroids or immunomodulators; and in patients with severe UC who have not responded to corticosteroids with or without 5-ASAs and with or without immunomodulators.

12.13 Members considered that an average of 40% of patients with moderate to severely active disease could be contraindicated to, intolerant of, or unresponsive to conventional therapies. Members considered that the number of patients with severe UC in New Zealand could be less than that proposed by the supplier.

12.14 The Committee noted that the supplier's 2013 application used placebo as a comparator, and the 2017 resubmission used infliximab as a comparator. The Committee considered that the appropriate, funded comparator is intravenous infliximab administered on a weight-based dosing schedule of 5 mg per kg initially, then at 2 and 6 weeks, then every 8 weeks. The Committee considered that it was unclear whether there is dose equivalence of adalimumab and infliximab at the dosages currently used for the treatment of UC.

12.15 The Committee noted that previous reviews of this application by PTAC had identified uncertainties regarding the optimal treatment of patients with moderate to severely active UC, and considered that the current body of evidence could not address all uncertainties.

12.15.1 The Committee considered that the optimal sequencing of treatments, dose and regimen (with or without therapeutic drug monitoring) and the most suitable location for administration eg. hospital outpatient setting or at home, was unclear.

12.15.2 Members considered that in clinical practice, colectomy use is decreasing since the wider introduction of biologics. The use of biologic agents eg. adalimumab and infliximab for UC may delay surgery, although it is unclear what impact delaying surgery has on the number of patients who proceed to colectomy, or on the quality of life of patients with UC.

12.15.3 The Committee noted that there is an increased risk of cancer with UC, and also an increased risk of cancer with long-term use of biologics, but considered it was unclear how delaying colectomy through longer use of biologics might change the risk of developing cancer due to increased exposure to the biologic. Members considered that the evidence suggests that treatment with biologics may convey some protective effect against cancer when used in other indications through earlier control of inflammation, but were unable to estimate the extent that such protection might translate and extend to the UC setting.

12.15.4 The Committee noted that new pharmaceuticals, (eg. ustekinumab and vedolizumab) and biosimilar adalimumab products are becoming available for the treatment of UC and clinical trials investigating these are underway.

12.15.5 Members noted that infliximab formulations for subcutaneous administration are becoming available, however, currently there is insufficient data to assess any differences in immunogenicity compared with intravenous administration.

12.16 The Committee noted that there was no new evidence from randomised controlled trials that have directly compared adalimumab with infliximab in moderate to severely active UC.

12.17 Members noted that there had been four indirect treatment comparisons carried out (Archer et al. Health Technol Assess. 2016:20;1-326, Danese et al. Ann Intern Med. 2014:160;704-11, Stidham et al. Aliment Pharmacol Ther. 2014:39;660-71, and Thorlund et al. J Crohns Colitis. 2014:8;571-81). Members considered that most of this data suggests that infliximab may provide more benefit than adalimumab as induction therapy, and that these agents may provide roughly equivalent benefit in the maintenance setting (although two of the meta-analyses suggest that maintenance with adalimumab may provide more benefit than infliximab maintenance). Members considered that these indirect comparisons may suggest that clinical outcomes at one year after induction may be equivalent for adalimumab and infliximab.

12.18 The Committee noted the two years of claims data provided by PHARMAC for infliximab usage in the 20 District Health Boards (DHBs).

12.18.1 The Committee noted that volume of infliximab used during the 2017 to 2019 financial years in each of the two available formulations (100 mg vial and 1 mg

for ECP) was pooled into a total infliximab volume in milligrams per DHB per financial year for all indications.

12.18.2 The Committee noted that the claims data classifying infliximab use as specifically for funded UC indications (severe ulcerative colitis and severe fulminant ulcerative colitis) was only available for the 6-month period from March 2019 to August 2019, due to indication data collection only starting in early 2019.

12.18.3 The Committee noted that these claims data show that infliximab is used to varying degrees at all 20 DHBs in New Zealand for the treatment of UC, however, the Committee was of the view that DHB infusion resources are at capacity levels and the variability in volume use may be due to access inequities.

12.19 The Committee noted an absence of information about the barriers to infliximab use in each DHB and considered that PHARMAC could approach DHBs to request information about any barriers to infliximab use at each DHB. Members considered that potential barriers to infliximab treatment could include patient location and ability to travel (due to requirement for hospital infusion for treatment administration), DHB infusion resource capacity, access to specialist care under a gastroenterologist, evolving surgical and pharmaceutical treatment paradigms in gastroenterology, and clinician and patient preferences including time commitment for treatment. The Committee considered that barriers to access to infusion services should not prevent a positive Committee recommendation for funding, but acknowledged that barriers may exist and may result in or exacerbate access inequities.

12.20 The Committee noted that a key benefit of adalimumab is convenience of administration. It was considered that if adalimumab were to be funded for moderate to severely active UC, some patients may receive infliximab for induction and then receive adalimumab for maintenance treatment.

12.21 The Committee considered that there was no evidence of superiority of adalimumab over infliximab in the first-line biologic treatment of moderate to severely active UC. However, the Committee considered that adalimumab is an acceptable alternative to infliximab and that it should be funded for first-line biologic treatment of moderate to severely active UC.

12.22 The Committee was not supportive of including the supplier-proposed additional prescribing options of “on the recommendation of a gastroenterologist or in accordance with a protocol or guideline that has been endorsed by the DHB Hospital” in the initial or renewal Special Authority criteria for adalimumab for the first-line biologic treatment of UC. The Committee noted that these proposed prescribing options would be inconsistent with the current, appropriate access criteria for adalimumab use in other indications.