PTAC Pharmacology and Therapeutics Advisory Committee

Objective advice to PHARMAC

Level 9, 40 Mercer Street, PO Box 10-254, Wellington 6143, New Zealand

Phone 64-4-460-4990 - Fax 64-4-460-4995 - www.pharmac.govt.nz

Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 18 & 19 February 2021

This meeting was held via videoconference, with the Chair and PHARMAC staff in attendance at PHARMAC office

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

Present: *3*

1. The role of PTAC, PTAC Subcommittees and meeting records **4**

2. Record of PTAC meeting held November 12 & 13 2020 **4**

3. Esketamine Email Discussion Record **4**

4. Subcommittee Records **5**

Anti-Infective Subcommittee (September 2020) *5*

Dermatology and Ophthalmology, Gastrointestinal and Rheumatology Subcommittees (October 2020) *7*

Cancer Treatment Subcommittee (October 2020) *7*

Respiratory Subcommittee (October 2020) *9*

Dermatology Subcommittee (November 2020) *10*

5. Correspondence & Matters Arising **12**

6. Perampanel for epilepsy **13**

7. Multiple Sclerosis treatments – amending access criteria to include the 2017 McDonald criteria **20**

8. Rivaroxaban for the prevention of major cardiovascular events **25**

9. Upadacitinib for moderate to severe rheumatoid arthritis **29**

Present:

Mark Weatherall (Chair for all items but one)
Alan Fraser
Brian Anderson
Bruce King
Elizabeth Dennett
Giles Newton Howes
Jane Thomas
Jennifer Martin
Lisa Stamp
Matthew Strother
Rhiannon Braund
Sean Hanna
Simon Wynn Thomas
Stephen Munn
Tim Stokes (member; acting Chair for one item)

Apologies

Marius Rademaker (Deputy Chair)

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

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

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

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

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

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

2. Record of PTAC meeting held November 12 & 13 2020

2.1. The Committee reviewed the record of the PTAC meeting held on 12 and 13 November 2020.

2.2. The Committee agreed with the record with the change in acronym from RMS to RRMS.

2.3. The Committee accepted the record.

3. Esketamine Email Discussion Record

3.1. The Committee noted and confirmed its email review of additional information submitted by the supplier of esketamine in relation to its application for treatment-resistant depression, as follows:

Application

3.2. The Committee reviewed correspondence in regard to the funding application for esketamine for the treatment of treatment-resistant depression (TRD).

Email Discussion

3.3. Pursuant to section 8.3 of the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016, the Committee considered the application for esketamine for the treatment of treatment-resistant depression (TRD) via email. All members who responded by email concurred with the following position. The Chair determined that the matter should be placed on the agenda of the Committee's February 2021 meeting to formally confirm the Committee's view.

3.4. The Committee noted that in February 2020, PTAC had considered a funding application for esketamine for the treatment of TRD.

3.5. The Committee noted that, in February 2020, PTAC had recommended the application for esketamine for the treatment of TRD be declined due to:

3.5.1. the evidence did not demonstrate a clear meaningful clinical benefit in differences between intervention and control groups in primary outcomes (reductions in end scores), combined with the relatively short duration of such trials in relation to the duration of depression;

3.5.2. the low strength of evidence in the New Zealand clinical setting due to the practical difficulties in implementing treatment with esketamine, in particular the health sector's capacity (time and skills) to diagnose treatment-resistant depression accurately; and the risk that this may delay patients with severe depression from accessing effective treatment that has a strong evidence base;

3.5.3. the risk of very high uptake based on a diagnosis of depression with suicidality, preventing access to other potentially more effective and established interventions;

3.5.4. the moderate to high risk to the individual and society regarding potential misuse or diversion despite the supplier's proposed risk management plan;

3.5.5. the absence of exit criteria in the supplier's proposed Special Authority or a clear clinical rationale for stopping treatment with esketamine, which could result in patients remaining on esketamine indefinitely; and

3.5.6. the uncertainty of potential long-term dependence and tolerance to esketamine.

3.6. The Committee noted that following the February 2020 recommendation, correspondence containing updated information was received from the supplier of esketamine. The Committee noted that the supplier requested that the priority recommendation be reconsidered given what the supplier stated to be the high unmet need, demonstration of esketamine as an effective agent in light of the updated information provided, and newly published long-term data from the SUSTAIN-2 phase 3 clinical trial.

3.7. The Committee noted that the SUSTAIN-2 study was a non-comparative cohort study and that the additional benefit of esketamine beyond conventional therapy could not be estimated.

3.8. The Committee considered that the new data provided did not address its previous concern that the magnitude of the additional change in depression score observed was unlikely to be clinically important.

3.9. The Committee considered that the additional information provided did not to address its previous concerns regarding the application and reiterated its previous recommendation to decline the application for esketamine for TRD.

4. Subcommittee Records

Anti-Infective Subcommittee (September 2020)

4.1. The Committee noted the record of the Anti-Infective Subcommittee of PTAC held on 22 September 2020.

4.2. The Committee noted that PTAC and PTAC Subcommittees may differ in the advice they provide to PHARMAC, including recommendations' priority, due to the committees' different, albeit complementary, roles, expertise, experience, and perspectives, and that PHARMAC would take into consideration both Committees' point of view in its assessment of this application.

4.3. In regard to item 5, hepatitis C:

4.3.1. The Committee noted that members of the Subcommittee considered that patients who do not experience sustained virologic response to direct acting antivirals could be considered, either for funding under the Named Patient Pharmaceutical Assessment (NPPA), or for listing on the Pharmaceutical Schedule, to enable treatment access to salvage options.

4.3.2. The Committee considered that the NPPA process may not necessarily be an appropriate mechanism of funding for these patients, due to lack of exceptionality.

4.3.3. The Committee noted that this group of patients may have particularly complex health needs due to NS5A/NS3 resistance.

4.3.4. The Committee noted that some of these patients may be accessing treatment through Professor Ed Gane.

4.3.5. The Committee noted that PHARMAC has processes in place in regard to the consideration/exploration of appropriate mechanism of funding medicines for such patient groups and recommended that PHARMAC staff explore this further and additionally seek advice about appropriate medicines and SA criteria, rather than using the NPPA process.

4.3.6. The Committee considered that the number of patients would be small but relatively predictable i.e. between 3 and 5% of those treated for Hepatitis C with anti-viral medication.

4.4. In regard to item 5, Antituberculotics and Antileprotics:

4.4.1. The Committee noted that the Subcommittee recommended linezolid be funded with a high priority for the treatment of multidrug-resistance tuberculous, based on updated World Health Organization guidelines for the treatment of multidrug-resistance tuberculous.

4.4.2. The Committee noted that for another WHO Group A agent, levofloxacin, which the Committee considered as second-line treatment for H. Pylori on the recommendation of the Gastrointestinal SC, there is currently no registered product in New Zealand.

4.4.3. The Committee agreed with the Subcommittee's high priority recommendation for the Linezolid recommendation.

4.5. In regard to item 5, urinary tract infections:

4.5.1. The Committee noted that the Subcommittee recommended that ciprofloxacin either be restricted to subsidy by endorsement or by Special Authority criteria for the indications already listed.

4.5.2. The Committee also noted that members of the Subcommittee suggested further restricting access to norfloxacin, to help prevent (or at least delay) the development of antimicrobial resistance to this agent.

4.5.3. The Committee noted that the addition of a Special Authority criteria may create barriers to care in groups experiencing health inequities. The Committee considered that it would be important to balance this with issues of antimicrobial resistance for these agents if criteria were introduced.

4.5.4. The Committee noted the Anti-Infectives Subcommittee's concerns regarding antimicrobial stewardship and suggested PHARMAC review the community Special Authority criteria for norfloxacin and ciprofloxacin.

4.6. In regard to item 7, rifampicin/isoniazid/pyrazinamide/ethambutol - fixed dose combination for tuberculosis:

4.6.1. The Committee noted the Subcommittee's high priority recommendation for this application.

4.6.2. The Committee noted that there would likely be a high degree of patient and clinician preference for a fixed-dose combination product.

4.6.3. The Committee noted that there was no evidence to suggest that the fixed-dose combination provided improved adherence or provided any other benefits over the multiple drug agents.

4.6.4. The Committee considered that in the New Zealand context, adherence to the multiple drug agents was unlikely to be the cause of tuberculosis-related death.

4.6.5. The Committee noted that based on international pricing, the fixed-dose combination product appeared to be cost-saving to the combined pharmaceutical budget. The Committee noted that there is currently no approved product in New Zealand, but **recommended** that rifampicin/isoniazid/pyrazinamide/ethambutol - fixed dose combination be funded if cost neutral to the individual agents.

4.6.6. The Committee noted that if pricing was not cost neutral, that PTAC or the Subcommittee should reconsider the application.

4.7. In regard to item 8, letermovir for cytomegalovirus infection prophylaxis:

4.7.1. The Committee **recommended** that the application be referred to the Transplant Immunosuppressant Subcommittee for review.

4.7.2. The Committee noted it would consider the Transplant Immunosuppressant Subcommittee's record prior to noting or agreeing with any recommendation for the application.

4.8. The Committee noted and **agreed** with the Anti-infective Subcommittee's recorded considerations and recommendations regarding the remaining items of the September 2020 meeting.

Dermatology and Ophthalmology, Gastrointestinal and Rheumatology Subcommittees (October 2020)

4.9. The Committee noted the records of the Dermatology and Ophthalmology combined Subcommittees of PTAC, Gastrointestinal Subcommittee of PTAC, and Rheumatology Subcommittee of PTAC discussions on the impact of a possible introduction of a biosimilar adalimumab, held on 8 October 2020, 13 October 2020 and 14 October 2020 respectively.

4.10. The Committee noted advice had been given to PHARMAC from a number of relevant speciality areas, and that PTAC had earlier reviewed evidence relating to a biosimilar adalimumab in November 2020.

4.11. The Committee considered the advice provided was consistent and noted no further comments.

Cancer Treatment Subcommittee (October 2020)

4.12. The Committee noted the record of the Cancer Treatments Subcommittee of PTAC (CaTSoP) meeting held on 15 and 16 October 2020, which included recommendations regarding the following funding applications;

- daratumumab (in combination with bortezomib & dexamethasone) for relapsed/refractory multiple myeloma,
- atezolizumab (in combination with paclitaxel, with or without bevacizumab) for the first-line treatment of non-small cell lung cancer (NSCLC),
- pembrolizumab for the first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC),
- sunitinib or pazopanib for good prognosis renal cell carcinoma (RCC),
- lenvatinib (in combination with everolimus) for the second-line treatment of metastatic RCC,
- lenvatinib for the treatment of radioactive iodine- refractory thyroid cancer,
- lenvatinib for the first-line treatment of unresectable hepatocellular carcinoma (HCC),
- trastuzumab emtansine for the treatment of HER2 positive early breast cancer,
- bendamustine for the treatment of relapsed/refractory Hodgkin's lymphoma, and
- durvalumab for unresectable NSCLC

4.13. The Committee noted that PTAC and PTAC Subcommittees may differ in the advice they provide to PHARMAC, including recommendations' priority, due to the committees' different, albeit complementary, roles, expertise, experience, and perspectives, and that PHARMAC would take into consideration both Committees' point of view in its assessment of this application.

4.14. In regards to Subcommittee record item 5 and CaTSoP's consideration of pembrolizumab for the first-line treatment of recurrent or metastatic HNSCC:

4.14.1. The Committee noted the Subcommittee's recommendation to decline this application. The Committee noted that this recommendation was, in part, due to the Subcommittee's consideration that the key clinical evidence for pembrolizumab showed uncertain long-term survival benefit in a patient population that differs substantially to the clinical population with HNSCC in New Zealand.

4.14.2. The Committee noted that CaTSoP suggested the Immunisation Subcommittee be asked for a review of the evidence for HPV vaccination in groups relevant to the New Zealand population. The Committee considered this would be important, and that specific advice could be to identify populations sub-groups that might have the greatest need and potential to benefit.

4.15. In regards to items 6 and 7 and CaTSoP's consideration of tyrosine kinase inhibitors e.g. sunitinib, pazopanib, lenvatinib:

4.15.1. The Committee noted the Subcommittee's recommendations, and also that it had suggested a broader review of the RCC treatment landscape in New Zealand and internationally, including with feedback from specialist groups such as the Genitourinary cancers special interest group.

4.16. In relation to item 10 and CaTSoP's consideration of trastuzumab-emtansine for the treatment of HER2 positive early breast cancer in patients who have residual disease after neoadjuvant systemic treatment:

4.16.1. The Committee noted the Subcommittee's recommendation that this be funded with a high priority within the context of treatments of malignancy and resolved that based on CaTSoP's assessment of the application against PHARMAC's Factors for Consideration, the Committee would change its earlier priority recommendation for this application from low to now become **medium**.

4.16.2. The Committee considered that there remained residual uncertainty regarding the use of trastuzumab in the metastatic setting following prior use of trastuzumab-emtansine in the adjuvant setting. The Committee considered that if trastuzumab-emtansine were to be funded in this adjuvant setting then the Special Authority criteria

for trastuzumab should exclude re-treatment in the metastatic setting for patients who had received trastuzumab-emtansine in the adjuvant setting, unless those who would benefit from trastuzumab in the metastatic setting after adjuvant trastuzumab-emtansine could be clearly defined. The Committee considered that further advice should be sought from CaTSoP regarding this.

4.17. In relation to item 11 and CaTSoP's consideration of bendamustine for the treatment of relapsed/refractory Hodgkin's lymphoma:

4.17.1. The Committee noted the Subcommittee's recommendation that this be funded with a medium priority within the context of treatments of malignancy.

4.17.2. The Committee noted that this is patient group have usually received a number of different treatments and still have a high health need. The Committee considered that this treatment should not be used by patients who have already received a transplant.

4.18. In relation to item 12 and CaTSoP's consideration of durvalumab for unresectable non-small cell lung cancer (NSCLC):

4.18.1. The Committee noted the Subcommittee's recommendations that this be funded with a high priority within the context of treatments of malignancy and resolved that PTAC's recommendation would remain at medium priority for funding, noting as stated in the meeting record of August 2020 the relatively wide confidence interval for the survival benefit, the lack of evidence for health-related quality of life, and concerns about long-term adverse effects.

4.19. The Committee noted and agreed with the Subcommittee's recorded considerations and recommendations regarding the remaining items of the October 2020 meeting.

4.20. The Committee noted that PTAC and PTAC Subcommittees may differ in the advice they provide to PHARMAC, including recommendations' priority, due to the committees' different, albeit complementary, roles, expertise, experience, and perspectives, and that PHARMAC would take into consideration both Committees' point of view in its assessment of this application.

Respiratory Subcommittee (October 2020)

4.21. The Committee reported the following conflicts of interest with regard to this agenda item.

4.22. The Committee noted the record of the Respiratory Subcommittee of PTAC meeting held on 28 October 2020, which included recommendations regarding the following funding applications;

- fluticasone furoate /umeclidinium bromide/vilanterol trifenatate (Trelegy Ellipta) for patients with chronic obstructive pulmonary disease,
- budesonide/eformoterol inhalers (100/6 and 200/6; dry powder for inhalation and pressurised metered dose inhalers) be dispensed stat,
- budesonide/eformoterol metered dose inhaler (Symbicort Rapihaler 100/3),
- fluticasone furoate/vilanterol 200/25 mcg (Breo Ellipta 200) for patients with severe asthma,
- widening access to mepolizumab for patients with severe eosinophilic asthma and a blood eosinophil count of greater than 300 cells/µL,
- widening access to mepolizumab for patients with severe eosinophilic asthma to remove the ACT criterion,
- benralizumab for the treatment of severe eosinophilic asthma

4.23. In regards to Subcommittee record item 7 and the Respiratory Subcommittee's consideration of fluticasone furoate with umeclidinium bromide and vilanterol trifenatate for the treatment of chronic obstructive pulmonary disease:

4.23.1. The Committee noted its previous recommendation regarding fluticasone furoate with umeclidinium bromide and vilanterol trifenatate. The Committee noted the Subcommittee's recommendation to fund fluticasone furoate with umeclidinium bromide and vilanterol trifenatate if it was cost-neutral to the pricing of the same components received from multiple inhalers (fluticasone furoate/vilanterol trifenatate 100/25 [Breo Ellipta] in combination with umeclidinium [Incruse Ellipta]) within the context of respiratory disease. The Committee considered that the Respiratory Subcommittee's recommendation was more appropriate and agreed with its recommendation, and considered that it would be important for patients currently receiving triple therapy via multiple inhalers to be eligible for fluticasone furoate with umeclidinium bromide and vilanterol trifenatate, if funded.

4.24. In regard to item 9 and the Respiratory Subcommittee's consideration of fluticasone furoate/vilanterol 200/25 mcg for patients with severe asthma:

4.24.1. The Committee noted the recommendation to fund fluticasone furoate/vilanterol 200/25 mcg (Breo Ellipta 200) for the treatment of severe asthma with a medium priority within the context of respiratory disease.

4.24.2. The Committee discussed concerns regarding the proposed Special Authority criteria for access to fluticasone furoate/vilanterol 200/25 mcg. The Subcommittee considered that there may be a risk of slippage for this potentially large patient group. In addition, the Committee noted the potential risk of pneumonia associated with the use of high dose inhaled corticosteroids. The Committee noted that most asthma exacerbations would be managed in the community and considered there to be a risk of overprescribing.

4.24.3. The Committee considered that it would like to review the application to further consider the wider issues of this high dose inhaled corticosteroid. The Committee considered that its primary concern regarded the targeting of the most appropriate patient population. The Committee considered that it would be useful to review if available NZ-specific evidence for adverse events and the risk of slippage for high dose inhaled corticosteroids.

4.25. The Committee noted and agreed with the Subcommittee's recorded considerations and recommendations regarding the remaining items of the October 2020 meeting.

4.26. The Committee noted that PTAC and PTAC Subcommittees may differ in the advice they provide to PHARMAC, including recommendations' priority, due to the committees' different, albeit complementary, roles, expertise, experience, and perspectives, and that PHARMAC would take into consideration both Committees' point of view in its assessment of this application.

Dermatology Subcommittee (November 2020)

4.27. The Committee noted the record of the Dermatology Subcommittee of PTAC held on 25 November 2020, which included recommendations regarding the following funding applications:

- risankizumab for moderate to severe plaque psoriasis, and
- rituximab for pemphigus (all types).

4.28. The Committee noted that PTAC and PTAC Subcommittees may differ in the advice they provide to PHARMAC, including recommendations' priority, due to the committees' different, albeit complementary, roles, expertise, experience, and

perspectives, and that PHARMAC would take into consideration both Committees' point of view in its assessment of this application.

4.29. In regards to Subcommittee record item 6.2 and the Dermatology Subcommittee's consideration of the Special Authority restrictions for isotretinoin:

4.29.1. The Committee noted the Subcommittee's consideration of the importance in maintaining the funding restrictions of isotretinoin due to safety concerns. The Committee considered Schedule restrictions are primarily used to manage the financial impact of treatments and that the isotretinoin Special Authority criteria would likely be reviewed as part of PHARMAC's developing Schedule standards.

4.29.2. The Committee considered there were challenges presented by the isotretinoin Special Authority, primarily the difficulty in determining 'competency' of a prescribing clinician via Special Authority restrictions.

4.29.3. The Committee noted and agreed with the Subcommittee's suggestion that the renewal for isotretinoin could be removed, therefore resulting in lifetime approvals.

4.30. In regards to item 6.26 and 6.27 and the Dermatology Subcommittee's consideration of ivermectin for scabies:

4.30.1. The Committee noted the Subcommittee's recommendation to maintain the Special Authority restrictions for ivermectin and noted this agreed with the recommendation from the Anti-Infectives Subcommittee.

4.30.2. The Committee noted the World Health Organization (WHO) has recommended ivermectin for use in the treatment of scabies and that ivermectin for use the treatment of scabies was added to the Model List of Essential Medicines in 2019. The Committee considered this should be highlighted to the Dermatology Subcommittee at its next meeting.

4.31. In regards to item 7 and the Dermatology Subcommittee's consideration of risankizumab for moderate to severe plaque psoriasis:

4.31.1. The Committee reviewed the Subcommittee's discussion and recommendation, noting rizankizumab offered a different mechanism of action to currently funded plaque psoriasis treatments. The Committee considered the appropriate PASI treatment outcomes had changed since the Committee last considered an application for an agent used in the treatment of plaque psoriasis. The Committee considered it would be beneficial for PHARMAC's evaluation of this application if there was clear advice regarding the health utilities for this patient group and likely patient numbers and supporting evidence for these factors.

4.31.2. The Committee noted the evidence reviewed by the Subcommittee regarding the efficacy of rizankizumab and noted a head-to-head trial with adalimumab had been included in the application.

4.31.3. The Committee noted it had not previously reviewed an application for rizankizumab for any indications and considered it would typically review applications for a new biologic treatment.

4.31.4. The Committee reviewed the Subcommittee's recommendations and requested PHARMAC bring the application to PTAC for consideration. The Committee considered this was consistent with previous applications for new biologic treatments.

4.32. In regards to item 8 and the Dermatology Subcommittee's consideration of for rituximab for pemphigus (all types):

4.32.1. The Committee reviewed the Subcommittee's discussion of the application. The Committee considered the remission rates for rituximab in the treatment of pemphigus to be favourable against the comparators. The Committee considered the patient group to be small and well defined and that this group would usually be treated by a dermatologist.

4.32.2. The Committee noted and agreed with the Subcommittee's recommendation that rituximab for pemphigus be funded with a high priority, subject to the Special Authority criteria outlined by the Dermatology Subcommittee.

4.33. The Committee noted and agreed with the Subcommittee's recorded recommendations regarding the remaining items of the November 2020 meeting.

5. Correspondence & Matters Arising

Apalutamide correspondence (Janssen)

5.1. The Committee reviewed correspondence from Janssen that was received in December 2020 in relation to PTAC's review of its application for the funding of apalutamide for the treatment of high-risk, non-metastatic, castration resistant prostate cancer (HR nmCRPC).

5.2. The Committee noted feedback regarding the evaluation of the statistical methods utilised in the analysis of the SPARTAN trial. Members considered that there remained some concern regarding the alpha-spending (with potential false positive results) but considered that the survival analyses conducted to account for crossover of patients from the placebo to the apalutamide group did support an overall survival advantage for apalutamide in comparison to placebo. The Committee noted that this data has now been formally published in a peer-reviewed journal and considered that this could be used by PHARMAC in a cost-effectiveness analysis of apalutamide.

5.3. The Committee noted that the supplier had not provided data summaries that would support a critical appraisal of claims made regarding health-related quality of life for patients receiving apalutamide treatment.

5.4. The Committee considered that further advice should be sought from CaTSoP, as noted in the meeting records from February and September 2020, and that it may reconsider its recommendation after CaTSoP's review.

Gemtuzumab-ozogamicin correspondence (Pfizer)

5.5. The Committee reviewed correspondence from Pfizer that was received in December 2020 in relation to PTAC's review of CaTSoP's recommendation regarding its application for the funding of gemtuzumab-ozogamicin for the treatment of de novo acute myeloid leukaemia (AML).

5.6. The Committee clarified that it did not decline to provide a recommendation, but noted CaTSoP's recommendation for funding, and highlighted the uncertainties that related to the benefit that would occur with gemtuzumab-ozogamicin in this patient population.

5.7. The Committee noted that the overall survival benefit was difficult to assess in this population, however considered that in fact there was a survival benefit from gemtuzumab-ozogamicin treatment, as discussed in the European Medicines Agency review of gemtuzumab-ozogamicin for the treatment of AML (Ali, S. et al. The Oncol. 2019;24:e171-e179). The Committee noted the differences in dose between that recommended by CaTSoP and that referenced by the supplier. The Committee however considered that CaTSoP was best placed to provide advice regarding the appropriate dosing for gemtuzumab-ozogamicin in this clinical group.

6. Perampanel for epilepsy

Application

6.1. The Committee reviewed the following applications for perampanel in the treatment of epilepsy:

6.1.1. An application from Eisai New Zealand Ltd for the adjunctive i.e. additional add-on, treatment of partial-onset seizures (POS) with or without secondary generalised seizures in adult and adolescent patients from 12 years of age with epilepsy; and

6.1.2. An application from Eisai New Zealand Ltd for the adjunctive (add-on) treatment of primary generalised tonic-clonic (PGTC) seizures in adult and adolescent patients from 12 years of age with idiopathic generalised epilepsy; and

6.1.3. A clinician application for use of perampanel in refractory epilepsy, most commonly focal epilepsies but also in complex myoclonic epilepsies.

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

Recommendation

6.3. The Committee **recommended** that perampanel for the treatment of partial onset (focal) seizures (POS) be funded with a medium priority, subject to Special Authority criteria.

6.3.1. In making this recommendation, the Committee considered: the health need of patients with epilepsy; the disproportionate impact of epilepsy on Māori and Pacific peoples; the strong, high quality evidence for perampanel versus placebo (from direct comparator randomised controlled trials) and moderate strength, medium quality evidence for perampanel versus lacosamide (indirect comparisons) reporting a benefit with perampanel; the side effect profile of perampanel; the advantage of once daily dosing which would be reduced in the context of multiple medicines for epilepsy; and the uncertainty regarding optimal positioning of perampanel within New Zealand treatment paradigms for epilepsies.

6.4. The Committee **recommended** that perampanel for the treatment of primary generalised tonic-clonic (PGTC) seizures be funded with a low priority, subject to Special Authority criteria.

6.4.1. In making this recommendation, the Committee considered: the health need of patients with epilepsy; the disproportionate impact of epilepsy on Māori and Pacific peoples; the strong, high quality evidence for perampanel versus placebo (one randomised controlled trial and an observational study), and weak, low quality evidence for perampanel versus other AEDs (indirect comparisons) reporting a reduction in seizures with perampanel; the side effect profile of perampanel; the advantage of once daily dosing which would be reduced in the context of multiple medicines for epilepsy; and the uncertainty regarding optimal positioning of perampanel within New Zealand treatment paradigms for epilepsies.

6.5. The Committee **recommended** that perampanel for the treatment of complex myoclonic epilepsy be funded with a low priority, subject to Special Authority criteria.

6.5.1. In making this recommendation, the Committee considered: the high health need of the small group of patients with complex myoclonic epilepsy, in particular; the disproportionate impact of epilepsy on Māori and Pacific peoples; the evidence of a reduction in seizures with perampanel (noting that high-quality evidence would not be

forthcoming in this small patient group); the side effect profile of perampanel; the advantage of once daily dosing which would be reduced in the context of multiple medicines for epilepsy; and the uncertainty regarding optimal positioning of perampanel within New Zealand treatment paradigms for epilepsies. The Committee considered that, if funded for complex myoclonic epilepsy, Special Authority for perampanel would need to tightly define the population with complex myoclonic epilepsy in order to effectively target funding to this group.

6.6. The Committee considered that advice regarding the applications for perampanel should be sought from the Neurological Subcommittee and/or other experts in this field especially regarding the following particular aspects: ascertaining where complex myoclonic epilepsy fits into the diagnostic and therapeutic pathway; the optimal positioning of perampanel within New Zealand treatment paradigms for epilepsies; appropriate dosing and stopping criteria for funded perampanel treatment; monitoring requirements for patients on perampanel treatment; and proposed Special Authority criteria.

Discussion

6.7. The Committee noted that the incidence of epilepsy in New Zealand is estimated to be around 0.05%, equivalent to six people being diagnosed per day, with prevalence of about 1% in the population (roughly equivalent to about 50,000 people with epilepsy) (Ministry of Health, 2019). The Committee noted that Māori and Pacific people are disproportionately affected by epilepsy, with both groups experiencing higher hospital admission rates due to epilepsy and Māori experiencing greater mortality from epilepsy than non-Māori (National Minimum Dataset, August 2019).

6.8. The Committee noted that that the supplier considers that approximately 60% of all patients with epilepsy in New Zealand have partial-onset seizures (POS), also known as focal seizures, resulting in an estimated 26,691 patients in New Zealand with POS in epilepsy.

6.9. The Committee noted that generalised tonic-clonic (GTC) seizures can be described as primary (PGTC) or secondary, particularly in POS with secondary generalisation. The Committee noted that the supplier had estimated approximately 30% of patients with epilepsy in New Zealand have PGTC seizures, equivalent to approximately 13,300 patients in New Zealand in 2020.

6.10. The Committee noted that complex seizures are defined as seizure activity associated with altered consciousness. The Committee noted that the clinician application described uncommon syndromes, such as Unverricht-Lundborg disease and Lafora disease, which cause complex myoclonic epilepsy that is associated with progressive myoclonic seizures. Members considered that the small group of patients with complex myoclonic epilepsy would be a subtype of the population with POS or epilepsy syndromes and are distinct from the group of patients with PGTC seizures.

6.11. The Committee noted that sudden unexplained death in epilepsy (SUDEP) is 40 times more likely among patients with epilepsy who continue to have seizures than in those who are seizure free disease, and that epilepsy significantly affects many activities especially driving. The Committee noted that epilepsy can also have an adverse effect on employment and is associated with risks and adverse outcomes in pregnancy. The Committee considered that patients with PGTC seizures and those with POS experiencing secondary GTC seizures have a high health need due to the impact on their daily activities and an increased requirement for hospital visits due to seizures.

6.12. Members considered that the relatively small number of patients with indeterminate epilepsy or other syndromes, as per International League Against Epilepsy (ILAE) definitions (Scheffer et al. Epilepsia. 2017;58:512-21), and patients with epilepsy

secondary to other conditions e.g. primary or secondary tumours, strokes, head injury or infection, which were not included within the applicant-proposed patient groups, may have an unmet health need.

6.13. The Committee noted that there are 16 funded anti-epileptic drugs (AEDs) in New Zealand, and that the suitability of an AED for a particular patient may be influenced by known side effects e.g. exacerbating myoclonus, risks associated with pregnancy, and long-term effects that prescribers are well aware of. The Committee noted that the treatment paradigm in New Zealand as outlined by the supplier for POS and PGTC seizures is as described in 8.14.1 and 8.14.2 below, and considered that, although this may differ from that followed in routine practice for treatment of POS and PGTC (e.g. phenytoin is infrequently used, and valproate may not be used as an initial treatment), the treatment paradigm for patients with complex myoclonic epilepsy would be similar to that for patients experiencing POS:

6.13.1. Patients with POS receive valproate, topiramate and levetiracetam as first, second and third-line AEDs, respectively; then carbamazepine, lamotrigine and/or phenytoin as fourth and fifth-line AEDs; then lacosamide as a sixth line treatment (all funded without restriction except lacosamide); and

6.13.2. Patients with PGTC seizures receive first-line treatment with valproate, then second-line treatment includes the addition of, or substitution for, levetiracetam, lamotrigine, topiramate or clobazam (all funded without restriction).

6.14. The Committee noted that refractory or drug resistant epilepsy is defined by the ILAE as not obtaining seizure freedom after adequate trials of two tolerated appropriate AED schedules; while the medical literature suggests up to 25% of patients with epilepsy would meet this definition, in New Zealand this could be about one-third of all patients with epilepsy (Epilepsy Technical Advisory Group, Ministry of Health. 2017). The Committee considered that drug resistant epilepsy would include patients with either POS or PGTC seizures. Members considered that patients who are severely affected by drug resistant epilepsy have a high health need and require additional treatment options.

6.15. The Committee considered that while estimated patient numbers provided by the supplier were reasonable and seizure types were clearly defined, it may be challenging to consistently distinguish and characterise patients for the purposes of targeting funded treatment. The Committee considered that PHARMAC could seek advice from the Neurological Subcommittee and/or other expert advisors regarding the optimal positioning of perampanel, if it were to be funded, within New Zealand treatment paradigms for epilepsies.

6.16. The Committee noted that perampanel is a first-in-class molecule that is a selective, non-competitive antagonist of the AMPA (ionotropic α-amino-3hydroxy-5-methyl-4-isoxazoleproprionic acid) type glutamate receptor on post-synaptic neurons; this mechanism of action is different to that of many other AEDs which instead interact with the sodium channel. Members considered that, due to the different mechanism of action, clinicians may have a preference to use perampanel relatively early in the treatment paradigm over additional sodium channel blockers. The Committee noted that perampanel may interact with other AEDs and is teratogenic.

6.17. The Committee noted that perampanel is an oral tablet taken once daily at night, and is approved by Medsafe for the adjunctive treatment of adult and adolescent patients from 12 years of age with epilepsy who have either POS with or without secondary generalised seizures, or PGTC seizures in patients with idiopathic generalised epilepsy.

6.18. The Committee noted the following evidence for perampanel for the treatment of POS from double-blind, placebo-controlled, multicentre phase III clinical trials in patients ≥12 years of age with POS with or without secondary generalisation, whose epilepsy had failed treatment with two or more AEDs, who had at least five partial seizures during baseline and who were taking stable doses of up to three approved AEDs:

6.18.1. Study 304: A randomised (1:1:1) study of 388 patients experiencing a median of 12.0-14.3 seizures per 28 days who received perampanel 8 mg or perampanel 12 mg or placebo once daily (French et al. Neurology. 2012;79:589-96). The Committee noted that the median change in seizure frequency was -26.3% with perampanel 8 mg (P=0.0261 rank ANCOVA; log transformation-based ANCOVA P=0.044), -34.5% with perampanel 12 mg (P=0.0158 rank ANCOVA log transformation-based ANCOVA P=0.0184) and -21.0% with placebo (nil placebo patients lost to follow-up); that the differences in 50% responder rates were not statistically significant for 8 mg or 12 mg perampanel; and that quality of life changes were similar between groups.

6.18.2. Study 305: A randomised (1:1:1) study in 386 patients experiencing a median of 11.8-13.7 seizures per 28 days who received perampanel 8 mg or perampanel 12 mg or placebo once daily (French et al. Epilepsia. 2013;54:117-25). The Committee noted that the median change in seizure frequency was -30.5% with perampanel 8 mg (P<0.001 rank ANCOVA; log transformation-based ANCOVA P=0.001), -17.6% with perampanel 12 mg (P=0.011 rank ANCOVA log transformation-based ANCOVA P=0.025), and -9.7% with placebo. The Committee noted that the 50% responder rates were 33.3% with perampanel 8 mg (P=0.002), 33.9% with perampanel 12 mg (P<0.001) and 14.7% with placebo and no differences in the changes in quality of life between the placebo and perampanel-treated groups were reported.

6.18.3. Study 306: A randomised (1:1:1:1) study in 712 patients experiencing a median of 9.3-10.9 seizures per 28 days who received perampanel 2 mg or perampanel 4 mg or perampanel 8 mg or placebo once daily (Krauss et al. Neurology. 2012;78:1408-15). The Committee noted that the median % change in seizure frequency was -13.6% with perampanel 2 mg (P=0.420 rank ANCOVA), -23.3% with perampanel 4 mg (P=0.003 rank ANCOVA), -30.8% with perampanel 8 mg (P<0.001 rank ANCOVA), and -10.7% with placebo. The Committee noted that the 50% responder rates were 20.6% with perampanel 2 mg (P value not reported), 28.5% with perampanel 4 mg (P=0.013), 34.9% with perampanel 8 mg (P<0.001), and 17.9% with placebo.

6.18.4. Study 335: A randomised (1:1:1:1) study in 704 patients who received perampanel 4 mg or perampanel 8 mg or perampanel 12 mg or placebo once daily (Nishida et al. Acta Neurol Scand. 2018;137:392-99). The Committee noted that the median changes in seizure frequency were −17.3% with perampanel 4 mg (P=0.2330), −29.0% with perampanel 8 mg (P=0.0003), −38.0% with perampanel 12 mg (P<0.0001), and −10.8% with placebo.

6.18.5. Study 307: An extension study including 1,218 patients with uncontrolled simple or complex POS, +/- secondary generalization, despite treatment with 1–3 approved anti-epileptic drugs who received once daily double-blind treatment with perampanel or placebo in the phase III 304, 305 and 306 studies, who then went on to receive adjunctive perampanel once daily titrated to a maximum dose of 12 mg per day (Krauss et al. Epilepsia. 2013;54:126-34; Krauss et al. Epilepsia. 2014;55:1058-68; Krauss et al. Epilepsia. 2018;59:866-76). The Committee noted a high rate of discontinuation over time in the open-label extension with some due to adverse events or inadequate therapeutic effect. Members considered it possible that perampanel has waning efficacy over time. The Committee noted that the responder rate and median change in seizure frequency with ≥3 years exposure to perampanel (N=436) were 59.6% and 62.0%, respectively; the responder rate and median change

in seizure frequency with ≥4 years exposure (N=78) were 67.9% and 70.6%, respectively.

6.19. The Committee noted the perampanel dose was increased in 2 mg increments during a six-week titration period followed by a 13-week maintenance period in studies 304, 305, 306 and 335.

6.20. The Committee noted that, due to the absence of head-to-head trials directly comparing perampanel with lacosamide in patients with POS, the supplier had provided an indirect treatment comparison using data from the following four, randomised, double-blind, placebo-controlled trials of lacosamide (note 600 mg per day lacosamide dose was not included in the indirect analysis due to the lack of registration for this dose). The Committee considered that the evidence from these trials was generally comparable without any significant differences in trial design and the conclusion that perampanel is non-inferior to lacosamide appeared reasonable.

6.21. The Committee noted the results of an open-label, single-arm study of adjunctive perampanel oral suspension in 180 children with inadequately controlled focal seizures or generalised tonic-clonic seizures, which suggested that daily oral adjunctive perampanel treatment is generally safe, well tolerated and efficacious in this group of children aged 4 to 12 years (Fogarasi et al. Epilepsia. 2020;61:125-37).

6.22. The Committee noted the following evidence for perampanel for the treatment of PGTC seizures in patients aged ≥12 years:

6.22.1. Study 332: A multicentre, randomised (1:1), placebo-controlled, double-blind, parallel-group study of 162 patients experiencing a median of about 2.5 PGTC seizures per 28 days with idiopathic generalised epilepsy who received perampanel 8 mg once daily or placebo, with dosing increased in 2 mg increments during a four-week titration period followed by a 13-week maintenance period (French et al. Neurology.2015;85:950-7). The Committee noted that the change in PGTC seizure frequency per 28 days was -76.5% with perampanel 8 mg versus -38.4% with placebo (P<0.0001) and the 50% PGTC seizure responder rate was 64.2 with perampanel 8 mg versus 39.5 with placebo (P=0.0019).

6.22.2. Study 32 open-label extension: A single-arm, open-label extension study of 138 patients who completed the double-blind phase of Study 332 and received either placebo (N=70) or perampanel (N=68), who then received once-daily perampanel (≤12 mg/day) for a six-week blinded conversion period and then ≥136 weeks maintenance (Wechsler et al. Neurology. 2017;88 (16_Suppl) P5.233). The Committee noted that the change in seizure frequency was −100.0% with placebo and −93.1% with perampanel, and the 50% responder rate was 74.3% with placebo and 75.0% with perampanel.

6.22.3. GENERAL: A multicentre, retrospective, one-year observational study in 149 patients with idiopathic generalised epilepsy who were prescribed perampanel, median dose 6 mg for a mean duration of 12.1 months (Villanueva et al. Epilepsia. 2018;59:1740-52). The Committee noted that the study population experienced a mixture of primary tonic-clonic seizures, POS and secondary GTC seizures, that many patients had previously or were currently receiving a large number of AEDs at baseline (N=17 receiving 7 AEDs or more), and that at the study endpoint a large number of patients were receiving levetiracetam, lamotrigine or zonisamide in particular, in combination with perampanel. The Committee noted that, at 12 months, 88 (59.1%) of participants were free of all seizures and 72 (62.6%) were free of generalised tonic-clonic seizures for at least the previous six months, and there was a mean 77.8% relative reduction in seizure frequency from baseline.

6.23. The Committee noted that the supplier had provided an indirect treatment comparison that used six studies with interventions including gabapentin, levetiracetam, lamotrigine, lamotrigine-XR, topiramate and perampanel to assess the comparative clinical efficacy and safety of perampanel and alternative AEDs used as adjunctive treatment in the management of PGTC seizures (IMS Health, 2015). The Committee noted that none of the reported differences reached statistical significance, however, perampanel performed numerically better than lamotrigine, levetiracetam and gabapentin in the proportion of patients with a PGTC seizure response. The Committee considered that this indirect comparison suggested similar efficacy and safety with perampanel.

6.24. The Committee also noted evidence from a meta-analysis of AED trials for patients (N = 921) with drug-resistant idiopathic generalised epilepsy, which suggested perampanel is associated with a 50% or greater reduction in seizures (Colleran et al. Seizure. 2017;51:145-56), although the Committee considered this meta-analysis could be at high risk of bias; and a systematic literature review of adjunctive anti-epileptic drug trials in patients with PGTC seizures illustrates changes in standard of care over 12-20 years (Tsong et al. Value in Health 2015;18:A722-A3).

6.25. The Committee noted that participants in the perampanel POS trials (304, 305, 306, 335 and 307) and in the perampanel PGTC seizure trials (332 and GENERAL) were balanced between trial treatment arms, the trials included a mix of seizure types e.g. some secondary generalised seizures, and there were no participants from New Zealand. The Committee noted that minimal data regarding quality of life including important activities such as driving and working, or SUDEP was collected, and no hospitalisation data was reported.

6.26. The Committee considered that freedom from seizures, an outcome not included in the perampanel trials, would be a more clinically meaningful outcome than a reduction in seizures, especially in the context of high baseline numbers of seizures, and that the translation of the trial outcomes into clinical meaning was unclear.

6.27. The Committee considered that the reduction in the number of seizures reported in the randomised phase III perampanel trials indicated an effect of perampanel compared with placebo, and that although the differences in responder rate between groups in study 304 were not statistically significant, study 305 appeared to repeat this experiment and reported statistically significant differences between treatment arms. The Committee considered that the effect of perampanel on seizure reduction was also seen in the open-label extension.

6.28. The Committee noted that the perampanel trials provided some data to suggest that quality of life was higher in patients whose disease responded to perampanel compared to those who did not get a response, however, the Committee noted that the perampanel trials did not have sufficient statistical power to test quality of life, and considered they provided poor quality of life data overall.

6.29. The Committee noted the following evidence for perampanel for the treatment of myoclonic seizures in patients with complex myoclonic epilepsy:

6.29.1. A retrospective study of perampanel efficacy and tolerability in 31 patients with myoclonic seizures and average epilepsy duration of 18 years and who had previously taken an average of 5.03 AEDs (Gil-Lopez et al. Acta Neurol Scand. 2018;138:122-9). Patients with other seizure types in addition to myoclonic seizures were allowed; generalised tonic clonic seizures were reported in 17 (54.8%) and focal in 1 (3.2%). At six months, 15 (48.4%) of the 31 patients were classed as myoclonic seizure responders, 10 (32.3%) were myoclonic seizure free, and 39% saw improvements in functional ability. The Committee considered that these results

indicated a benefit from perampanel in this setting, noting that a third of patients were seizure-free.

6.29.2. Case series of 12 patients with Unverricht-Lundborg disease who received perampanel add-on therapy, of which ten had a clear clinical response of myoclonus and generalised tonic-clonic or myoclonic seizures stopped in all six patients who had still experienced them (Crespel et al. Epilepsia. 2017;58:543-7).

6.29.3. Case report of perampanel as add-on therapy persistent myoclonus and generalised tonic-clonic seizures with Lafora disease, where seizure control was achieved (Schorlemmer et al. Epilepsy Behav Case Rep. 2013;1:118-21).

6.29.4. Review articles regarding early clinical experience with perampanel for focal epilepsy (Trinka et al. Acta Neurol Scand. 2016;133:160-72), perampanel in drug-resistant epilepsy (Frampton J. Drugs. 2015;75:1657-68), and the broad-spectrum potential of perampanel (Potschka & Trinka. Epilepsia. 2019;60 Suppl 1:22-36).

6.30. The Committee noted that the clinician-provided evidence included the patient population with drug resistant epilepsy who have complex myoclonic epilepsy and experience focal seizures in particular; however, the Committee considered that the group described in this evidence spanned both the supplier-defined POS and PGTC seizure groups.

6.31. The Committee was made aware of evidence that perampanel may cause euphoric effects and therefore may contain a risk of abuse (Shih et al. Ther Clin Risk Manag. 2013; 9: 285–293), and was made aware of evidence of rare but serious reports of suicidal and homicidal ideation associated with perampanel treatment (Ettinger et al. Epilepsia. 2015;56:1252-63), noting that a total of seven cases of suicidal ideation were reported in study 306 and 307. The Committee noted that the Study 307 open-label extension also reported a high incidence of adverse events (87.4%) including severe events e.g. SUDEP or epilepsy-related death. The Committee noted the treatment-emergent adverse events including worsening of seizures and psychiatric events were reported by the perampanel trials, and considered that although some severe events were reported, the side effect profile of perampanel was generally comparable with that of other AEDs.

6.32. The Committee considered that the evidence for perampanel seemed applicable to the New Zealand population with drug resistant epilepsy, and that patients with drug resistant epilepsy and POS or PGTC may benefit from perampanel. The Committee considered that there was:

6.32.1. Strong, high quality evidence for perampanel versus placebo from randomised controlled trials and moderate strength, medium quality evidence for perampanel versus lacosamide from indirect comparisons, of a benefit for patients with POS who were treated with perampanel; and

6.32.2. Strong, high quality evidence for perampanel versus placebo, and weak, low quality evidence for perampanel versus other AEDs from indirect comparisons, suggesting a reduction in seizures with perampanel for patients with PGTC seizures; and

6.32.3. Weak and low-quality evidence from case reports suggesting a reduction in seizures and a proportion of patients becoming seizure free with perampanel for patients with complex myoclonic epilepsy (which the Committee considered to be a subtype of the group with POS). Members considered that this evidence was clinically relevant and meaningful given the high health need of patients with complex myoclonic epilepsy, as higher quality data would not likely be available in this relatively small population group.

6.33. The Committee noted that the supplier claimed once-daily dosing of perampanel ay be advantageous, however, the Committee considered that this benefit would be diminished in the context of adjunct treatment of drug resistant epilepsy where patients would likely be taking other AEDs with different, potentially more frequent, dosing schedules.

6.34. The Committee considered that the assumptions underlying the supplier-provided cost-effectiveness modelling for both POS and PGTC seizures, respectively, were generally reasonable, although it was unclear how applicable the quality of life and medical resource data were to the New Zealand setting. The Committee noted that study 332 efficacy data were extrapolated for PGTC seizure modelling and the number of prior AEDs in their model was higher than the number of prior AEDs used by participants in the 332 trial.

6.35. The Committee considered that the supplier applications had underestimated the possible morbidity due to side effects of perampanel, especially due to psychiatric adverse events. The Committee considered that this treatment-related morbidity would have an impact on the health system resource due to the cost and complexity of managing side effects from perampanel, which would drive health system costs and be less likely to provide net savings to the health system. The Committee noted that there was no evidence to support the claim that perampanel could reduce health system resource usage, in particular hospital admission duration or emergency department visits. The Committee considered that well-controlled epilepsy resulting in freedom from seizures would be expected to convey a reduction in carer responsibility and an increase in patient employment, although no evidence was provided to quantify these possible benefits from treatment with perampanel.

6.36. The Committee considered that use of perampanel as a fifth or sixth-line treatment for drug resistant epilepsy in patients aged 12 years and older may be reasonable, and that perampanel would be used in combination with other AEDs, especially newer AEDs. However, the Committee considered that the corresponding patient population who would benefit most from perampanel given its side effect profile (which would include those with complex myoclonic epilepsy) was poorly defined, and that it was unclear where perampanel should be located within the funded treatment paradigm for epilepsies in New Zealand.

6.37. The Committee considered that the appropriate comparators for cost-effectiveness assessment were unclear as these are not disease-specific and would depend on the location of perampanel in treatment paradigms. The Committee considered that lacosamide in combination with another AED may be an appropriate comparator for POS. The Committee considered that reduced seizure frequency and mortality risk reduction were appropriate outcomes to model for POS and PGTC seizures.

6.38. The Committee considered that advice from the Neurological Subcommittee and/or other experts in this field should be sought regarding the appropriate location of perampanel in treatment paradigms, in addition to appropriate dosing and stopping criteria for funded perampanel treatment, monitoring requirements for patients receiving perampanel, and proposed Special Authority access criteria (noting that the supplier-proposed criteria would likely enable access for patients with complex myoclonic epilepsy).

7. Multiple Sclerosis treatments – amending access criteria to include the 2017 McDonald criteria

Application

7.1. The Committee reviewed the application for amending multiple sclerosis access criteria to include the 2017 McDonald criteria.

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

Recommendation

7.3. The Committee recommended that the access criteria for multiple sclerosis treatments be widened to include the 2017 McDonald criteria with a medium priority, subject to the following Special Authority criteria:

Entry Criteria

1. Diagnosis of multiple sclerosis (MS) must meet the McDonald 2017 diagnostic criteria for MS and be confirmed by a neurologist. Diagnosis must include MRI confirmation; and
2. Patient must have an EDSS score 0 - 6.0; and
3. Patient has had at least 1 significant attack of MS in the previous 12 months or 2 significant relapses in the past 24 months; and
4. All of the following:
    a. Each significant attack must be confirmed by the applying neurologist or general physician (the patient may not necessarily have been seen by them during the attack, but the neurologist/physician must be satisfied that the clinical features were characteristic); and
    b. Each significant attack is associated with characteristic symptom(s)/sign(s) or substantially worsening of previously experienced symptoms(s)/sign(s); and
    c. Each significant attack has lasted at least one week and has started at least one month after the onset of a previous attack; and
    d. Each significant attack can be distinguished from the effects of general fatigue; and is not associated with a fever (T> 37.5°C); and
        i. Each significant attack is severe enough to change either the EDSS or at least one of the Kurtze Functional System scores by at least 1 point; or
        ii. Each significant attack is a recurrent paroxysmal symptom of multiple sclerosis (tonic seizures/spasms, trigeminal neuralgia, Lhermitte's symptom); and
5. Evidence of new inflammatory activity on an MR scan within the past 24 months; and
6. Any of the following:
    i) A sign of that new inflammatory activity is a gadolinium enhancing lesion; or
    ii) A sign of that new inflammatory activity is a lesion showing diffusion restriction; or
    iii) A sign of that new inflammatory is a T2 lesion with associated local swelling; or
    iv) A sign of that new inflammatory activity is a prominent T2 lesion that clearly is responsible for the clinical features of a recent relapse that occurred within the last 2 years; or
    v) A sign of that new inflammatory activity is new T2 lesions compared with a previous MR scan.

Renewal

Only from a neurologist or general physician. Approvals valid for 12 months where patient has had an EDSS score of 0 to 6.0 (inclusive) at any time in the last six months (i.e. the patient has walked 100 metres or more with or without aids in the last six months).

7.4. The Committee made this recommendation based on the high health need of people with multiple sclerosis (MS) who ultimately progress, the health benefits of earlier access to disease modifying treatments and good quality research. The Committee also took into account the potential risk of toxicity from lifelong treatment of patients who may never go on to develop clinically definitive MS and the lack of apparent short-term benefits for patients.

7.5. The Committee considered that it would be interested in the results of a sensitivity analysis increasing the time horizon in the cost utility model, provided that robust, data-driven assumptions are made around the long-term impact of the change in access criteria. The Committee noted it could revisit its recommendation following the availability of this information.

Discussion

7.6. The Committee noted an application from the Multiple Sclerosis Treatments Advisory Committee (MSTAC) to amend access criteria for initiation of disease-modifying treatments (DMTs) for MS to include patients with only one clinical episode (clinically isolated syndrome, or CIS) but who fulfil McDonald 2017 revised multiple sclerosis diagnostic criteria (Thompson et al. Lancet Neurol. 2018;17:162-73).

7.7. The Committee noted that a funding application for MS treatments for CIS fulfilling the McDonald 2010 diagnostic criteria was declined by PTAC in 2014, and that it would review its recommendation should new evidence become available.

7.8. The Committee noted that in 2017, a funding application was recommended for decline by PTAC for widened access to multiple sclerosis treatments to include patients who with CIS who fulfil the McDonald 2010 diagnostic criteria for MS (but without the additional requirement to experience significant relapse in the preceding 12 months). The Committee noted that, at the time, Members considered that the evidence provided in support of the application consisted of low-quality evidence such as selected expert consensus statements and non-systematic evidence reviews that recommend early initiation, rather than high quality evidence such as randomised controlled trials and that some of the trials pre-dated the most recent revision of the McDonald diagnostic criteria (2010).

7.9. The Committee noted that when treatment for CIS was previously discussed, there was little epidemiological data of progression to clinically definite MS. The Committee noted that, since its previous review of treatment for CIS, the use of MRI has become more widespread, and more studies of better quality have been published indicating the benefit of treating patients with disease modifying treatments following a single clinical attack.

7.10. The Committee noted that CIS is the term used to describe the first episode of neurological symptoms that last for at least 24 hours and have no other cause (such as other illness, or fever), and that CIS may be the first sign of what may subsequently become clinically definite MS (usually relapsing remitting MS, often followed by progression to secondary progressive MS), and the ultimate risk of diagnosis of MS is higher after an episode of CIS than if there was no CIS. The Committee noted that carer burden for MS patients is associated with the degree of disability, and the economic and emotional state of the person with MS (Opara et al. Neurol Neurochir Pol. 2012;46:472-9).

7.11. The Committee noted that MS has a lower prevalence in the Māori population compared with the non-Māori population, and that incidence is not linked to socioeconomic status. The Committee noted, however, that MS patients in deprived socioeconomic circumstances have a more rapid progression of disease, which may be due to issues with access to treatment (Calocer et al. PLoS One. 2018;13:e0191646).

7.12. The Committee noted that key diagnostic criteria for MS are dissemination in time and dissemination in space, and that when this was purely clinically determined there was a requirement for more than one episode or attack. The Committee noted that since MRI technology has progressed, dissemination in space can be radiographically determined, and dissemination in time can be determined with the use of gadolinium or assumed by the presence of CSF-specific oligoclonal bands. The Committee noted that this is reflected in the updated 2017 McDonald criteria, and as such patients with only one clinical attack may fulfil these criteria and be diagnosed with MS. The Committee noted that the development of a second attack or clinically definite MS is the gold standard for validating the 2017 McDonald criteria.

7.13. The Committee noted a review summarising the data of different cohorts of MS patients to verify if the diagnosis of MS has been improved using the McDonald criteria of 2017 (Schwenkenbecher et al. Front Neurol. 2019;10:188). The Committee noted that the proportion of patients who developed clinically definite MS five years after being diagnosed at the CIS stage using the McDonald 2017 criteria varied significantly between studies – from a positive predictive value (PPV) of 44% in one study to 98% in another. The Committee considered that the differences in PPV between studies can be attributed to the fact that not all calculations are done based on a baseline evaluation

of the cohort. For example, van der Vuurst de Vries et al. (2018) reported a PPV of 64-69% at five years if all time points between baseline and the 5 years were considered, which decreased to 54% if only baseline evaluations are considered (van der Vuurst de Vries et al. 2018; JAMA Neurol. 2018;75:1392-8). Conversely, Lee et al. (2019) reported a PPV of 94%, however, the population only included those patients with evidence of dissemination in space on MRI at baseline (Lee et al. Eur J Neurol. 2019;26:540-45). The Committee noted that PPV also depends on if patients receive disease modifying treatment or not, as treatment may delay such progression. The Committee noted a study by Hyun et al (2019) that reported a PPV at 2 years of 70% for the entire patient population studied, which increased to 94% at two years for those who did not receive disease modifying treatment (Hyun et al. Mult Scler. 2019;25:1488-95).

7.14. The Committee noted that the McDonald 2017 criteria may have some ability to anticipate a second 'attack' and thereby predict clinically definite MS (CDMS), noting the widely variable PPVs reported in the literature. The Committee considered that treatment of patients defined by McDonald 2017 criteria would likely result in some patients receiving disease modifying treatments unnecessarily i.e. that some patients would never go on to develop clinically definitive MS, and considered that 14% would be an appropriate estimate for the New Zealand setting based on evaluable evidence from two studies (Hyan et al, van der Vuurst de Vries et al.) that separated out CIS patients who do not receive DMTs prior to the development of CDMS.

7.15. The Committee noted a study by Rae-Grant et al (2018), which compared the relative risk of conversion to MS over two years of different disease modifying treatments (Rae-Grant et al. Neurology. 2018;90:789-800). The Committee noted that all drugs investigated reduced the relative risk of progression with moderate to high confidence.

7.16. The Committee noted a long-term follow-up study of the randomised BENEFIT CIS trial, which investigated the outcomes for patients treated with interferon beta-1b immediately after CIS (Kappos et al. Neurology. 2016;87:978-87). The Committee noted that early treatment delayed the onset of clinically definite MS by 2.7 years when compared with delaying treatment (average delay 1.5 years). The Committee noted that there was no difference in Expanded Disability Status Scale (EDSS) score or health related quality of life between the early and delayed treatment arms. The Committee considered that disease progression from CIS and relapsing-remitting MS (when the EDSS score at treatment initiation is low, i.e. <3.5) would be expected to have slow progression in disability.

7.17. The Committee noted a study by Lazzaro et al (2009) on the economic evaluation of treating CIS and subsequent MS with interferon beta-1b (Lazzaro et al. Neurol Sci. 2009;30:21-31). The Committee noted that the study reported that early treatment of all CIS patients with interferon beta-1b was highly cost-effective. The Committee noted a study by Brown et al. (2019) investigating the progression of patients from relapsing-remitting MS to secondary progressive MS (Brown et al. JAMA. 2019;321:175-87). The Committee noted that all disease modifying treatments investigated in the study made a difference and delayed disease progression, but that the newer disease modifying treatments appeared more effective (fingolimod, alemtuzumab, natalizumab). The Committee noted that initiating treatment with disease modifying treatments within five years of relapsing-remitting MS also significantly slowed the progression to secondary progressive MS.

7.18. The Committee noted a 2019 study by Harding et al. outlining the clinical outcomes of escalating treatment versus early intensive disease modifying treatment in MS patients (Harding et al. JAMA Neurol. 2019;76:536-41). The Committee noted that that time to sustained accumulation of disability was longer for patients who were treated with early intensive disease modifying treatments, compared to patients who were started on less intense treatments and were escalated as their disease progressed. The Committee

noted that the escalation approach is what is currently implemented in New Zealand for the treatment of MS. The Committee also noted evidence indicating that treating CIS patients with disease modifying treatments appears to reduce brain atrophy over time, and considered that this may delay eventual decrease in health-related quality of life experienced by MS patients (Tsivgoulis et al. PLoS One. 2015;10: e0116511).

7.19. The Committee considered that the strength and quality of evidence, including its relevance to New Zealand, for health benefits that may be gained from widening access to disease modifying treatments for patients with only one clinical episode but who fulfil McDonald 2017 criteria, was high for the benefits of early treatment; but considered that the heterogeneity of reported PPVs meant that the evidence for the predictive power of the McDonald criteria was modest at best, and noted that there are no New Zealand studies of PPV for McDonald 2017 criteria.

7.20. The Committee considered that the possible benefits of earlier treatment of MS i.e. at CIS presentation, include a delay in transition from CIS to clinically definite MS, reduced annualised rates of relapse, delayed transition to secondary progressive MS, and reduced brain atrophy. The Committee considered that early treatment of CIS patients who meet the McDonald 2017 criteria would likely provide some benefit to patients, especially when delivered within five years of disease onset. The Committee noted that early treatment effects may depend on the type of disease modifying treatment used, noting that newer agents are likely to be superior in regard to delaying or preventing the onset of secondary progressive MS. The Committee noted in the Brown et al. study that when glatiramer acetate or interferon beta were compared with newer agents (fingolimod, alemtuzumab or natalizumab) that the cumulative hazard of conversion to secondary progressive MS was slower with the newer agents (HR=0.66; 95% CI 0.44 to 0.99; P=0.046).

7.21. The Committee also considered the possible harms of treating patients with CIS, including the potential for unnecessary treatment with associated treatment-related harms, which could affect 2% to 66% of CIS patients diagnosed with MS using the McDonald 2017 criteria, as well as the cost associated with treating patients who would not benefit. The Committee considered that early treatment of CIS patients would have little effect on caregiver burden immediately, which would be low to begin with, due to the low level of disability at the CIS stage; however, that over time a delay in MS progression would also delay caregiver burden.

7.22. The Committee considered that whilst the McDonald 2017 criteria would only increase the early diagnosis of clinically definite MS by about 25% compared to current practice, the incorporation of the 2017 criteria into funding restrictions for disease modifying treatments would increase the prevalent population in a treatment cohort of CIS patients who might benefit from disease modifying treatments. The Committee considered that there would be approximately 40 additional patients in the first year, and 80 new patients in the following two years that would have access to disease modifying treatments if access were widened to CIS patients. The Committee noted that, according to Kappos et al., patients would be starting treatment approximately 1.5 years earlier than they would under the current criteria. The Committee noted that the proportion of CIS patients fulfilling McDonald 2017 criteria would increase over time, from 54% at baseline to 69% over 5 years, as additional patients fulfilled the criteria and others remained on treatment. The Committee also considered that the appropriate comparator for this patient population is no treatment, and that approximately 24% of CIS patients would be unnecessarily treated i.e. these patients would not progress to experiencing a relapse, at least within a five-year time horizon.

7.23. The Committee noted a report on the natural history of CIS, which outlined that 10 years from an episode of CIS, 35% of patients will not have progressed to clinically definite MS, but that the majority of CIS patients will go on to develop relapsing-remitting MS and then secondary progressive MS (Hou et al. Sci Rep. 2018;8:10857).

The Committee noted that, over time, more and more patients progress to clinically definite MS, and that by 30-40 years, very few patients have not progressed. The Committee considered that any true quality of life improvements or differences from earlier treatment would only be measurable over a lifetime time horizon, and that short term it would be unlikely that there would be any assessable quality of life benefit. The Committee expressed interest in any future sensitivity analysis results from cost utility analysis modelling, provided that robust, data-driven assumptions were made around the long-term impact of the change in access criteria. The committee considered that delays in transition to secondary progressive MS over a lifetime time horizon would be a key driver in differences in EDSS and HRQoL.

8. Rivaroxaban for the prevention of major cardiovascular events

Application

8.1. The Committee reviewed the application for rivaroxaban for the prevention of major cardiovascular events in patients with peripheral with or without coronary artery disease.

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

Recommendation

8.3. The Committee **recommended** that rivaroxaban for the prevention of major cardiovascular events in patients with peripheral artery disease be listed with a low priority subject to the following Special Authority criteria:

INITIAL APPLICATION
Applications from any relevant practitioner. Approvals valid for 12 months.
All of the following:
1. Patient has peripheral artery disease and
   1.1. Previous peripheral artery or carotid revascularisation intervention; or
   1.2. Asymptomatic stenosis $\geq$ 50% of the carotid artery diagnosed by angiography or non - invasive imaging; and
2. Patient must be prescribed rivaroxaban 2.5mg twice daily in combination with 100mg aspirin daily; and
3. Patient must not be in the period immediately following revascularisation when intensified antiplatelet therapy is indicated; and
4. Patient must not be on Dual Anti Platelet therapy

RENEWAL:
Applications from any relevant practitioner. Approvals valid for 12 months.
The treatment remains appropriate and the patient is benefiting from treatment.

8.4. The Committee made this recommendation based on:

- robust evidence of benefit from the pivotal trial (which was large and well designed) for this patient group, especially for stroke reduction;
- the high health need for this patient group;
- the risk of bleeding being present, although noting that this was mild and manageable,
- significant uncertainty regarding the patient numbers that would be eligible for rivaroxaban;
- the need to fund a reversal agent if rivaroxaban were to be funded for this patient group;
- concern regarding the appropriate dosing for patients in the New Zealand context, compared to the trial population, based on body weight.
- the Māori and Pacific population in New Zealand having a higher absolute risk of MACE due to the presence of comorbidities such as obesity.

8.5. The Committee **recommended** that advice be sought from the Cardiovascular Subcommittee regarding New Zealand patients who are considered to be at high risk

of major cardiovascular events due to peripheral/coronary artery disease, to define a high-risk population group, and to suggest suitable Special Authority criteria for that patient population.

Discussion

8.6. The Committee noted an application from Bayer for the use of rivaroxaban (Xarelto) for the first-line treatment of peripheral artery disease (PAD) with or without coronary artery disease (CAD). The Committee noted that rivaroxaban is currently open listed on the Pharmaceutical Schedule, but that there has been no previous review or consideration for the 2.5 mg formulation, or for the requested indication. The Committee also noted that rivaroxaban (2.5 mg) is Medsafe registered for the requested indication.

8.7. The Committee noted that PAD and CAD are clinical presentations of atherosclerosis, which is a progressive condition affecting the large and medium-sized arteries. PAD and CAD develop in different vascular beds but can frequently coexist in patients with multi-vessel disease. The Committee also noted that the main risk factors for atherosclerosis include lack of physical activity, smoking, unhealthy diet, age, and a family history of heart disease.

8.8. The Committee noted that PAD is caused by atherosclerosis of the arteries and mainly affects the lower extremities and sometimes the carotid arteries, and that PAD can include asymptomatic and symptomatic disease, the latter including intermittent claudication, chronic limb ischemia, and acute limb ischemia, which can lead to gangrene and amputation. The Committee noted that the unstable plaques in PAD can rupture and trigger acute atherothrombotic events because of embolus formation, such as myocardial infarction, stroke, cardiovascular death, and acute limb ischemia. The Committee noted that PAD is broadly defined as a progressive stenosis or occlusion of any of the arteries except the coronary and intracranial arteries, and that patients with PAD are more than 6 times more likely to have a heart attack or stroke, and 13 times more likely to have lower limb amputation. The Committee also noted that an estimated 50% of people with PAD in New Zealand are underdiagnosed, and undertreated, and that a significant proportion of patients are diagnosed late.

8.9. The Committee noted that CAD is caused by atherosclerosis of the coronary arteries, which leads to a restriction of blood flow to the heart, and can be categorised into acute coronary syndrome (refers to a range of conditions associated with a sudden, reduce blood flow to the heart including unstable angina and acute myocardial infarction) or chronic CAD (including patients with stable angina and patients who have survived acute limb ischemia and have 'restabilised' although patients remain at risk of recurrent major adverse cardiovascular events (MACE), which includes myocardial infarction, stroke and cardiovascular death).

8.10. The Committee noted that, in New Zealand, men experience PAD at a rate of 491 per 100,000, compared to 347 per 100,000 for women (Social Wellbeing Agency, 2013). The Committee also noted that Māori experience PAD at a rate of 269 per 100,000 compared to the non-Māori population's rate of 438 per 100,000. The Committee noted that Māori disproportionately experience death from stroke and have higher incidences of hospitalisation from total cardiovascular disease, ischemic heart disease, and lower limb amputation as a result of coronary disease. The Committee considered that the burden of PAD in the Māori population is likely greatly underdiagnosed, and significantly higher than reported. The Committee considered that there is an increased carer and financial burden on the families of patients with complications from PAD/CAD and MACE, especially in cases like stroke where patients may not be able to work or perform day to day tasks.

8.11. The Committee noted that the applicant had defined two patient groups in its application: the group of patients in the stable phase of PAD, and the subgroup with diagnoses of PAD and CAD (concurrent). The Committee considered that the PAD and CAD subgroup, should not be considered as a discrete group because patients are unlikely to have peripheral disease without coronary arteries also being affected. The Committee considered that the CAD subgroup would be reasonably representative of the combined PAD and CAD subgroups as both groups would present with CAD. Therefore, patients with CAD would be a surrogate of the PAD and CAD patient group intended by the supplier. The Committee considered that the Cardiovascular Subcommittee would be best placed to define a patient group at higher risk of MACE.

8.12. The Committee noted the phase III randomised controlled trial, COMPASS (Eikelboom et al. N Engl J Med. 2017;377:1319-30), in which adult patients with stable cardiovascular disease (PAD and/or CAD) were randomised to receive either rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily (n=9152), rivaroxaban 5 mg alone twice daily (n=9117), or aspirin 100 mg alone once daily (n=9126) for a mean duration of 23 months. The Committee noted that approximately 90% of patients had CAD, while 20% had PAD.

8.13. The Committee noted that rivaroxaban in combination with aspirin had a lower incidence of MACE when compared to aspirin alone (379 patients vs 496, respectively; HR=0.76; 95% CI 0.66 to 0.86; P<0.001), especially in the case of stroke (HR=0.58; 95% CI 0.44 to 0.76; p<0.001) but did not have a statistically significant impact on the incidence of myocardial infarction (HR=0.86; 95% CI 0.70 to 1.05; p=0.145). The Committee also noted that all-cause mortality was lower in the rivaroxaban with aspirin treatment group compared to with aspirin alone (HR=0.82; 95% CI 0.71 to 0.96; p<0.001), which included a significant difference in cardiovascular mortality (HR=0.78; 95% CI 0.64 to 0.96; p=0.02).

8.14. The Committee noted a COMPASS follow-on study investigating the effects of rivaroxaban on major bleeding events, and noted that there was an increased incidence in adverse events associated with bleeding in the rivaroxaban in combination with aspirin treatment arm compared to the aspirin alone group, but noted that the incidence of fatality from bleeding was not significantly different between the two groups (Eikelboom et al. J Am Coll Cardiol. 2019;74:1519-28).

8.15. The Committee noted that the pivotal trial (COMPASS) included a heterogeneous population, and that subsequent subgroup analyses had been published to investigate which population groups derive the most benefit. The Committee noted the COMPASS follow-on study was conducted to identify subsets of patients in COMPASS at higher risk of recurrent vascular events (Anand et al. J Am Coll Cardiol. 2019;73:3271-80). The Committee noted that patients were stratified by risk using REACH (REduction of Atherothrombosis for Continued Health) atherothrombosis risk score and CART (Classification and Regression Tree) analysis, which reported that high-risk patients using the REACH score were those with two or more vascular beds affected, history of heart failure, or renal insufficiency, and by CART analysis were those with ≥2 vascular beds affected, history of heart failure, or diabetes. The Committee noted that for patients with multi-vessel disease i.e. PAD with CAD, the absolute risk reduction for cardiovascular events was 6.02% (HR=0.64; 95% CI 0.51 to 0.81) versus 1.36% (HR=0.80; 95% CI 0.68 to 0.93) for patients with one vascular bed affected. The Committee noted that PAD in the lower limbs presents differently to PAD affecting the carotid arteries, and that PAD affecting lower limbs was poorly represented in this study.

8.16. The Subcommittee also noted the following studies in relation to the use of rivaroxaban 2.5 mg in combination with aspirin for the prevention on MACE in PAD and CAD patients:

- Connolly et al. Lancet. 2018;391:205-218

- Moayyedi et al. Gastroenterology. 2019;157:403-412.e5.
- Vanassche et al. Eur J Prev Cardiol. 2020;27:296-307
- Anand et al. J Am Coll Cardiol. 2018;71:2306-2315
- Fox et al. J Am Coll Cadriol. 2019;73:2243-2250
- Branch et al. Circulation. 2019;140:529-537
- Lamy et al. J Am Coll Cardiol. 2019;73:121-130
- Sharma et al. Circulation. 2019;139:1134-1145

8.17. The Committee considered the evidence to be of moderate strength and high quality. The Committee noted that there was no relevant quality of life data from the COMPASS trial available.

8.18. The Committee noted that the baseline characteristics for the participants in the COMPASS trial had an average age of 68 years, and average BMI of 28, approximately 21% reported tobacco use, 75% had hypertension, and 37.5% had diabetes. The Committee considered that this may not accurately reflect the New Zealand PAD population, specifically the Māori and Pacific PAD populations, as these population groups have disproportionately higher rates of obesity, smoking, and diabetes, risk factor characteristics that were not represented in the COMPASS trial. The Committee considered that the twice daily 2.5 mg dosing schedule from the COMPASS trial may not be as beneficial or effective in a patient population which has a higher average weight, and that patients with a higher BMI may have the same risk of bleeding events before any additional benefit is seen and considered that the Cardiovascular Subcommittee would be best placed to give advice on appropriate dosing for the New Zealand population. The Committee also considered that restricting access to rivaroxaban based on an ankle-brachial index (ABI) < 0.90 would likely restrict diabetic patients who often have an ABI over 1, and that this was not clinically appropriate as restriction criteria.

8.19. The Committee noted that although the COMPASS trial duration was 23 months, patients who responded to treatment would likely remain on treatment for life. The Committee noted that the COMPASS trial excluded patients who were at a high risk of major bleeding events and considered that this may mean that bleeding events will occur more frequently in the patient population proposed, where the average risk of major bleeding with likely be higher. The Committee considered, however, that clinicians are experienced with bleeding events of this nature and that these events are manageable. The Committee also noted that the COMPASS trial reported a decrease in bleeding events over time, especially after the first year, noting that those who experience bleeds are likely to cease treatment.

8.20. The Committee considered that, if rivaroxaban were to be funded for this indication, a reversal agent, such as coagulation factor and exanet alfa, would also have to be funded if needed due to life-threatening or uncontrolled bleeding caused by anticoagulation treatment. The Committee noted that rivaroxaban treatment, would be managed in both primary and secondary care settings and that the frequency of routine monitoring of this patient group with blood tests would not be affected.

8.21. The Committee noted that the eligible population in New Zealand is likely to be greater than 20,000 patients, due to undertreatment and underdiagnosis of PAD and CAD in the New Zealand population. The Committee considered that the eligible patient population based on the inclusion criteria from the COMPASS trial could be up to 50,000 and that the uptake would be rapid. The Committee considered that, due to potentially large patient numbers, it may be more effective to restrict the patient population to patients classified as being at a high risk of MACE, as this population group also showed an increased benefit from treatment compared with patients with only one vascular bed affected. The Committee considered that considerations regarding patient numbers, uptake rates, and target patient groups should be confirmed by the Cardiovascular Subcommittee.

8.22. The Committee considered that advice should be sought from the Cardiovascular Subcommittee regarding appropriate classification of 'high-risk' patients, appropriate Special Authority access criteria for that population, numbers of eligible patients, an estimated rate of uptake, and the possible risk of slippage beyond the defined Special Authority group.

9. Upadacitinib for moderate to severe rheumatoid arthritis

Application

9.1. The Committee reviewed the application from AbbVie for upadacitinib (Rinvoq) for the treatment of moderate to severe rheumatoid arthritis. The Committee noted that the supplier's initial application was made in May 2019 and a subsequent addendum with additional, updated information was provided in May 2020.

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

Recommendation

9.3. The Committee **recommended** that upadacitinib be funded for the treatment of moderate to severe rheumatoid arthritis in patients for whom treatment with conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) has not been adequate, as a first-line biologic/targeted treatment instead of a currently funded first-line biologic DMARD i.e. adalimumab and etanercept, with a medium priority, subject to appropriate Special Authority criteria. This would include use of an alternative first-line biologic/targeted treatment following an inadequate response to or intolerable side effects from the other medicine(s) as permitted by current Special Authority criteria.

9.4. The Committee **recommended** that upadacitinib be funded for the treatment of moderate to severe rheumatoid arthritis in patients for whom treatment with current first-line biologic disease-modifying anti-rheumatic drugs (DMARDs) (adalimumab and/or etanercept) has not been adequate, as a second-line biologic/targeted treatment instead of currently funded second-line biologic DMARDs i.e. infliximab or rituximab, with a medium priority, subject to appropriate Special Authority criteria.

9.4.1. In making these recommendations, the Committee considered the high health need of this patient group for whom currently funded DMARD and biologic treatments fail or are intolerable; the evidence of benefit from upadacitinib in this population; the convenience of an oral formulation over current subcutaneous and intravenous treatments, which has the potential to help address access inequities e.g. for rural patients, and ease pressures on infusion services; and the requirement for a funded herpes zoster vaccine in this patient group.

9.5. The Committee considered that advice from the Rheumatology Subcommittee should be sought regarding upadacitinib for the treatment of RA, and in particular: whether there is evidence for the use of upadacitinib in children with juvenile idiopathic arthritis (JIA) and which particular types; the appropriate sequencing of upadacitinib and other treatments for RA; appropriate Special Authority criteria for upadacitinib for RA; and whether there is a class effect among JAK inhibitors in this setting.

Discussion

9.6. The Committee noted that rheumatoid arthritis (RA) is a debilitating chronic inflammatory autoimmune disease. The Committee noted that RA is diagnosed

clinically and that if untreated or unresponsive to therapy, inflammation and joint destruction lead to loss of physical function, inability to carry out daily tasks, and employment difficulties. The Committee noted that patients with RA have an increased risk of earlier death from all causes and have higher mortality from respiratory or cardiovascular diseases compared to people without RA.

9.7. The Committee considered that New Zealand epidemiology data were limited, but noted that the overall prevalence of diagnosed RA is about 2.6%, equivalent to about 101,000 adults (over 15 years of age) with RA (Ministry of Health, New Zealand Heath Survey 2018-19). The Committee noted that Māori, Pacific peoples and Asian populations are also affected by RA, with 2016/2017 prevalence of 2.3% in Māori (2018/2019 prevalence of 1.9%), 1.4% in Pacific peoples and 1.3% in Asian populations.

9.8. The Committee was made aware of evidence that indicated the magnitude of the health-related quality of life (HRQOL) impact from RA is similar to that of other chronic conditions such as type 2 diabetes, chronic heart failure and clinical depression (Smolen et al. Nat Rev Dis Primers. 2018;4:18001). The Committee noted that a high Disease Activity Score (DAS) indicates active RA, whereas a low DAS indicates a state of almost complete remission, and members considered that the HRQOL of patients with RA and a low DAS is similar to individuals without RA. The Committee noted that the DAS28-CRP measure, which is used in many RA clinical trials, is a composite measure of C-reactive protein (CRP) and of inflammation in 28 joints, although it excludes the small joints of the feet which are commonly involved in RA. The Committee considered that the ACR70 is a useful measure of disease response to treatment in RA clinical trials and is more desirable than the ACR20 or ACR50.

9.9. The Committee noted the intention for early, intensive treatment of RA to prevent joint damage and maintain quality of life. The Committee noted the aim of treatment is disease remission or a state of low disease activity. The Committee noted that initial treatment of RA in New Zealand typically uses conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs); initially with methotrexate alone and increasing to triple therapy if needed (or as initial treatment for severe presenting disease) with the addition of sulfasalazine and hydroxychloroquine, then using leflunomide with or without methotrexate if disease remission is not achieved. The Committee considered that co-prescribed leflunomide and methotrexate is not commonly used in other markets i.e. US and Europe, likely due to the increased risk of toxicity. For patients with disease of a severity that meets the relevant funding restriction criteria, first-line biologic DMARDs (adalimumab or etanercept, usually with methotrexate) and second-line biologic DMARDs (infliximab, rituximab and tocilizumab) may be used, with some patients cycling between these treatments within each line to achieve and maintain disease control, even if this disease control is suboptimal. The Committee considered a severe disease state is required to access funded biologic DMARDs (bDMARDs). The Committee noted prednisone may be taken by patients throughout the treatment paradigm for RA if required.

9.10. The Committee considered that the patient population with moderate to severe RA that has been failed by all funded treatments will continue to increase over time, and considered that these patients have an ongoing need for new and effective funded treatments. The Committee considered that patients with moderate to severe RA for whom tumour necrosis factor (TNF) inhibitors i.e. adalimumab, etanercept and infliximab, are contraindicated due to heart failure would be eligible to receive rituximab or tocilizumab, which are administered by intravenous infusion and therefore imparts a greater cost on patients, family/whānau and the health system compared with subcutaneous adalimumab or etanercept.

9.11. The Committee noted that upadacitinib is a selective and reversible inhibitor of JAK1, a member of the Janus kinase (JAK) family of enzymes, which is inhibited more

potently by upadacitinib than JAK2 and JAK3; this action interrupts the IL-6 signalling pathway, which is involved in inflammation and the immune response. Members considered that this potent inhibition of JAK1 may be responsible for differences in safety and efficacy between inhibitors of JAK1 and of JAK2. The Committee noted upadacitinib is a targeted synthetic DMARD (tsDMARD).

9.12. The Committee noted that AbbVie's brand (Rinvoq) of upadacitinib, an oral tablet taken one daily at a dose of 15 mg, is Medsafe registered for the treatment of adults with moderately to severely active RA, as monotherapy or in combination with methotrexate or other csDMARDs. The Committee noted the application requested funding for the 15 mg daily dose in particular. The Committee noted that upadacitinib is proposed by the applicant to be funded as a first- or subsequent-biologic/targeted treatment instead of currently funded first-line biologics i.e. adalimumab and etanercept. The Committee noted PHARMAC had also requested consideration of upadacitinib as a second-line bDMARD/tsDMARD, following an inadequate response to treatment with a first-line bDMARD, typically adalimumab.

9.13. The Committee noted that another JAK inhibitor, tofacitinib, targets JAK1 and JAK3 and that a funding application for tofacitinib for the treatment of active RA was considered by PTAC in August 2019 and is currently ranked. At that time, PTAC recommended that tofacitinib be funded with a medium priority for patients with RA under the same Special Authority criteria in place for adalimumab and etanercept, and also that it be funded with a medium priority for patients with moderate to severe RA who were not adequately responding to TNF inhibitors, subject to Special Authority criteria recommended by the Rheumatology Subcommittee.

9.14. The Committee noted that the key evidence for upadacitinib in adults with RA comes from five clinical trials:

9.14.1. SELECT-EARLY (van Vollenhoven et al. Arthritis Rheumatol. 2020;72:1607-20): A randomised (1:1:1), double-blind, phase III study (n=947) investigating once-daily doses of upadacitinib 15 mg or 30 mg or weekly methotrexate (7.5–20 mg per week) for 24 weeks, within a 48-week active comparator-controlled period followed by a four-year open-label extension for methotrexate-naïve patients aged ≥18 years with active, early RA i.e. RA symptoms for at least 6 weeks. Patients were excluded if they had prior intolerance of methotrexate or any prior exposure to a JAK inhibitor or bDMARD. The Committee noted the trial's ACR70 and DAS28-CRP results indicated that both doses of upadacitinib were superior to methotrexate when used as a first-line DMARD, but noted that this setting was not the requested placement for upadacitinib according to the application.

9.14.2. SELECT-MONOTHERAPY (Smolen et al. Lancet. 2019;393:2303-11): A randomised (2:2:1:1), placebo-controlled, double-blind phase 3 trial (n=648) examined the efficacy and safety of upadacitinib as monotherapy in patients aged ≥18 years with active RA and inadequate response to methotrexate after three or more months. Patients either switched to once-daily upadacitinib monotherapy (15 mg or 30 mg), or continued methotrexate at their existing dose as blinded study drug until week 14 where they were switched to 15 mg or 30 mg once-daily upadacitinib.

9.14.2.1. The Committee noted patients were excluded from SELECT-MONOTHERAPY if they had received a bDMARD or JAK inhibitor prior. Members considered that the trial population had relatively low active joint counts (>6) compared to New Zealand patients who are required to have a greater number of active joints (at least four large joints or 20 active joints) to be eligible under the proposed Special Authority criteria.

9.14.2.2. The Committee noted that at week 14, an ACR20 response was achieved by 68% (95% CI:62-74) receiving upadacitinib 15 mg, 71% (95% CI: 65-77)

upadacitinib 30 mg, and 41% (95% CI 35-48) in the continued methotrexate group (P<0.0001 for both doses vs continued methotrexate); however, members considered that the 20% improvement demonstrated by the ACR20 was not clinically meaningful.

9.14.2.3. The Committee noted that at week 14 the DAS28-CRP score of 3.2 or lower was met by 42/216 (19%) in the continued methotrexate group, 97/217 (45%) with upadacitinib 15 mg, and 114/215 (53%) with upadacitinib 30 mg (P<0.0001 for both doses vs continued methotrexate), and considered this indicated either dose of upadacitinib was more effective than methotrexate monotherapy in biologic-naïve patients.

9.14.3. SELECT-NEXT (Burmester et al. Lancet. 2018;391:2503-12): A randomised (2:2:1:1), double-blind, placebo-controlled phase 3 trial (n=661) examined the safety and efficacy of upadacitinib in patients aged ≥18 years with active RA, who had an inadequate response to one or two csDMARDs. Patients received a background csDMARD and either once-daily extended-release upadacitinib 15 mg or 30 mg, or placebo, for 12 weeks; then placebo patients received 15 mg or 30 mg of upadacitinib once daily.

9.14.3.1. The Committee noted that patients who had an inadequate response to prior bDMARD were excluded, however, up to 20% of patients were allowed to have previously used one bDMARD for up to three months and discontinued due to intolerance but not inefficacy.

9.14.3.2. The Comittee noted that at week 12 a ACR20 response was achieved by 64% with upadacitinib 15 mg and 66% with upadacitinib 30 mg, compared with 36% with placebo (P<0.0001 for each dose vs placebo), and DAS28-CRP score of 3.2 or less was met by 107 (48%), 105 (48%) and 38 (17%), respectively (P<0.0001 for each dose vs placebo). The Committee noted that the patient-reported outcomes including the Health Assessment Questionnaire Disability Index (HAQ-DI), a standard tool in trials of RA, indicated better improvement in quality of life with upadacitinib compared to placebo. The Committee considered that this evidence indicated that both doses of upadacitinib were better than placebo in terms of disease remission.

9.14.4. SELECT-COMPARE (Fleischmann et al. Arthritis Rheumatol. 2019;71:1788-800; Fleischmann et al. Ann Rheum Dis. 2019;78:1454-62): A randomised (2:2:1), double-blind, parallel-group, placebo-controlled and active comparator-controlled trial (n=1,629) that investigated upadacitinib 15 mg once daily, or adalimumab 40 mg every other week, or matching placebo, with stable background methotrexate for 48 weeks in patients aged ≥18 years with active RA who have previously received an inadequate response to methotrexate.

9.14.4.1. The Committee noted that patients who had an inadequate response to prior bDMARD or had prior exposure to a JAK inhibitor were excluded, however, up to 20% of patients were allowed to have previously used for up to three months, or not tolerated, one bDMARD except for adalimumab. The Committee noted that at baseline about 10% of patients had received a prior bDMARD; about 60% were receiving an oral glucocorticoid (mean dose of about 6 mg, based on prednisone or equivalent daily dose); patients had substantial erosion and the baseline DAS28-CRP was nearly 6, which members considered was quite high. The Committee considered that the COMPARE trial population was similar to the population of New Zealand patients with active RA who have previously received an inadequate response to methotrexate.

9.14.4.2. The Committee noted that the treatment in COMPARE aligned with use in the setting of first-line bDMARDs (adalimumab or etanercept, with methotrexate) in the New Zealand treatment paradigm for adult patients with RA.

9.14.4.3. The Committee noted that at week 26, significantly more patients who received upadacitinib achieved a remission compared with adalimumab or placebo (P≤0.001) and that the HAQ-DI improved more with upadacitinib than with adalimumab or placebo.

9.14.4.4. The Committee noted that the COMPARE trial included rescue-switching to another trial treatment for patients experiencing an inadequate response at week 14; the Committee noted that data reporting outcomes up to 24 weeks post-switch suggested that upadacitinib was more effective than other treatments, this was observational data and the length of time on treatment pre-switch was variable.

9.14.4.5. The Committee noted that, of patients in COMPARE who experienced an infection, the exposure-adjusted rate (per 100 patient-years) of herpes zoster infection was 3.1 (95% CI: 2.2 to 4.2) with upadacitinib vs 1.3 (95% CI: 0.5 to 2.8) with adalimumab.

9.14.5. SELECT-BEYOND (Genovese et al. Lancet. 2018;391:2513-24): A randomised (2:2:1:1), double-blind phase 3 trial (n=499) examined the safety and efficacy of upadacitinib in patients aged ≥18 years with active RA with previous inadequate response from or intolerance to at least one bDMARD after at least three months. Patients received once-daily oral extended-release upadacitinib 15 mg or 30 mg or placebo for 12 weeks, followed by upadacitinib 15 mg or 30 mg from week 12 onwards, with 1-2 concomitant background csDMARDs.

9.14.5.1. The Committee noted that patients were excluded from SELECT-BEYOND if they had received a JAK inhibitor prior and that while most participants had previously used one bDMARD, some had used two or three previously. Members noted that about three-quarters of participants received methotrexate and a large proportion received prednisone; members considered this was similar to what would be expected for New Zealand adult patients with RA.

9.14.5.2. The Committee noted that the treatment in SELECT-BEYOND aligned with use in the setting of second-line bDMARDs (infliximab, rituximab and tocilizumab) in the New Zealand treatment paradigm for RA.

9.14.5.3. The Committee noted that at week 12 a DAS28-CRP score of 3.2 or less was achieved by 71/164 (43%) of patients receiving upadacitinib 15 mg and 70/165 (42%) receiving upadacitinib 30 mg versus 24/169 (14%) of patients receiving placebo (P<0.0001 for each dose vs placebo). The Committee also noted the week 12 and 24 ACR20, ACR50 and ACR70 results as reported by the authors, and considered that SELECT-BEYOND indicates upadacitinib is effective when used after a bDMARD in patients with active RA.

9.15. The Committee also noted the following evidence for upadacitinib:

- Wang et al. Mayo Clin Proc. 2020;95:1404-19
- Rubbert-Roth et al. N Engl J Med. 2020 15;383:1511-21
- Kerschbaumer et al. Ann Rheum Dis. 2020;79:744-59
- Nader et al. Clin Pharmacol Ther. 2020;107:994-1003
- Sepriano et al. Ann Rheum Dis. 2020;79:760-70
- Olivera et al. Gastroenterology. 2020;158:1554-73.e12
- Cantini et al. Expert Opin Drug Saf. 2020;19:861-72

- Edwards et al. Rheumatol Ther. 2020. doi: 10.1007/s40744-020-00257-w. [Epub ahead of print]

9.16. The Committee noted that the five SELECT trials provide good evidence for efficacy of upadacitinib in RA, although limited switching data was available and there were no head-to-head trials with biologics except adalimumab. The Committee considered that the data suggested a likely class effect in terms of ACR70 and DAS28-CRP benefit from JAK inhibitors in moderate to severe RA, however, updated review of the evidence for tofacitinib in this population would be beneficial to inform assessment of a class effect. The Committee considered that advice from the Rheumatology Subcommittee should be sought regarding whether there is a class effect among JAK inhibitors in this setting.

9.17. The Committee considered that the evidence suggests upadacitinib may provide a greater benefit than adalimumab in this population, and was made aware of indirect evidence that suggests upadacitinib plus methotrexate appears more effective than adalimumab, however tofacitinib plus methotrexate appears not superior to adalimumab (Tice et al. Institute for Clinical and Economic Review. 2020). The Committee considered that there is evidence of a greater benefit from upadacitinib compared with methotrexate in patients with moderate to severe RA, and that upadacitinib monotherapy is effective in this patient population.

9.18. The Committee noted that it was difficult to determine whether upadacitinib would provide the same or similar therapeutic outcome as oral tofacitinib for patients with moderate to severe RA. However, the Committee noted two indirect comparison network meta-analyses for ACR and DAS28-CRP outcomes after 12 and 24 weeks of combination treatments including JAK inhibitors compared to conventional synthetic and bDMARDs; these report a higher ordinal surface under the cumulative ranking curve (SUCRA) ranking for upadacitinib than for other treatments including tofacitinib, indicating a higher probability that upadacitinib is preferred, although this was not indicative of any difference in magnitude of treatment effect and some results were not statistically significant (Pope et al. Adv Ther. 2020;37:2356-72; Lee et al. Z Rheumatol. 2020;79:785-96). Members considered that if only one of these agents (tofacitinib or upadacitinib) were funded for moderate to severe RA in New Zealand, upadacitinib may be preferred as the indirect evidence shows a trend towards superiority over tofacitinib, although this was highly uncertain based on the evidence to date. The Committee considered the Rheumatology Subcommittee would be best placed to consider the evidence and the potential class effect of JAK inhibitors. Members considered that the funding of either upadacitinib or tofacitinib would help address an unmet need for patients who were unable to achieve optimal disease response on currently funded treatments.

9.19. The Committee considered that although the evidence suggests an initial period of durable response, loss of benefit may be seen with upadacitinib in RA and this loss of benefit would be likely to be due to the complex nature of RA rather than anti-drug antibodies (ADAs), which can be a limiting factor for treatment benefit with TNF inhibitors but would not be expected with upadacitinib.

9.20. The Committee noted there was limited evidence for switching and sequencing of upadacitinib and other treatments for RA, and considered that it was unclear whether upadacitinib would provide the greatest benefit when used in the first-line or second-line and what the optimal sequencing of bDMARDs and tsDMARDs would be for this patient population, although observational data suggests that upadacitinib is effective when used after adalimumab. The Committee considered that, if upadacitinib were funded for use in any line, given the available evidence, it could be appropriate for a decision on its use to be at the clinician's and patient's discretion. The Committee considered that advice from the Rheumatology Subcommittee should be sought regarding appropriate sequencing of upadacitinib and other treatments for RA.

9.21. The Committee considered that the evidence suggests there is a class effect for adverse events from JAK inhibitors, and was made aware of evidence for both doses of upadacitinib from the five SELECT trials in which there was a statistically significant increased risk of herpes zoster (shingles) with upadacitinib compared with methotrexate (hazard ratio [HR] 2.997 and 3.023 for 15 mg and 30 mg, respectively) and adalimumab (HR 3.221 and 4.989, respectively) (Cohen et al. Ann Rheum Dis. 2020;annrheumdis-2020-218510; Supplementary Table S4). The Committee noted that a live attenuated herpes zoster vaccination e.g. Zostervax is contraindicated in patients receiving biologic treatment, therefore a non-live vaccine e.g. Shingrix, would be required in the patient population receiving a biologic treatment for RA.

9.22. The Committee noted that, like tocilizumab, upadacitinib is associated with elevated HDL and LDL cholesterol levels which can convey an increased lifetime risk of cardiovascular disease (CVD) for some patients, although it was unclear whether this was a clinically significant risk in the context of RA. The Committee was made aware of a meta-analysis of 26 randomised controlled trials that included almost 12,000 patients who received JAK inhibitors including upadacitinib, which reported that the increase in risk of CVD was not significant (Xie et al. Ann Rheum Dis. 2019;78:1048-54). The Committee considered that although this may not be a significant risk, lipid monitoring may be appropriate during treatment with upadacitinib.

9.23. Members noted that the safety profile of upadacitinib was otherwise as expected for JAK inhibitors, without an increased risk of pulmonary embolism seen with use of higher doses of tofacitinib (as used in the treatment of inflammatory bowel disease).

9.24. The Committee noted that the oral formulation of upadacitinib would offer suitability benefits in terms of convenience and ease of administration compared with subcutaneous (which require syringe disposal) or intravenous administration. The Committee considered that, if funded, use of upadacitinib would reduce the infusion resource required for the treatment of patients with moderate to severe RA, noting that infusion services in New Zealand are used for treatment of many conditions and currently operate at or near capacity.

9.25. The Committee noted that some formulations e.g. oral, offer advantages over others e.g. injection, for paediatric patients, although no evidence for the use of upadacitinib in juvenile idiopathic arthritis (JIA) was identified at this time. The Committee considered that advice from the Rheumatology Subcommittee should be sought regarding whether there is evidence for the use of upadacitinib and other JAK inhibitors e.g. tofacitinib, in children with JIA, and considered that a small group of children who have tried all other treatment options may seek funded access to upadacitinib.

9.26. The Committee noted that additional blood tests e.g. for lipid monitoring, and the cost of a non-live shingles vaccine should be included in the overall cost of upadacitinib treatment. The Committee considered that, if upadacitinib were funded, there would likely be a reduction in both the number of patients on first-line TNF inhibitors (adalimumab and etanercept) and the number of patients requiring IV-administered treatments for RA. The Committee considered that, in a second-line setting, it was uncertain whether upadacitinib would primarily be used after failure of one or two TNF inhibitors, and that the Rheumatology Subcommittee could advise on upadacitinib's place in the treatment algorithm and appropriate Special Authority access criteria for upadacitinib for RA.

9.27. The Committee noted the patient numbers estimated by PHARMAC staff, which assumed an expansion in the population receiving biologic or tsDMARD treatment of 10%, and high early uptake reflective of a bolus of patients moving onto upadacitinib treatment. The Committee considered that the assumptions used by PHARMAC staff in the budget impact analysis were reasonable and consistent with prior clinical advice, and would likely be similar for tofacitinib. The Committee considered that there may be

high uptake of oral tablets, and this would be driven by patient preference; the Committee also considered that, if funded with the same access criteria as adalimumab and etanercept, upadacitinib may be prescribed for greater than 40% of biologic-naïve patients with RA.

9.28. The Committee considered that, if upadacitinib were funded for use in any line of therapy for RA, a small number of patients currently on other therapies may elect to switch from their current therapy to upadacitinib; possibly due to poorly managed disease despite other treatment, or reliance on another person e.g. a nurse, for treatment administration.
