Record of the Rheumatology Advisory Committee Meeting held on 28 March 2023

Rheumatology Advisory Committee records are published in accordance with the Terms of Reference for the Specialist Advisory Committees 2021.

Note that this document is not necessarily a complete record of the Rheumatology Advisory Committee meeting; only the relevant portions of the meeting record relating to Rheumatology Advisory Committee discussions about an application or Pharmac staff proposal that contain a recommendation are generally published.

The Rheumatology Advisory Committee 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 Advisory Committees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Advisory Committee meeting will be reviewed by PTAC at an upcoming meeting.

Specialist Advisory Committees and PTAC may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

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 Specialist Advisory Committees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

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1. Attendance

Present
Rhiannon Braund (Chair)
Andrew Harrison
Janet Hayward
Keith Colvine
Michael Corkill
Priscilla Campbell-Stokes
Will Taylor

Apologies
Alan Fraser
Elizabeth Dennett

2. Summary of recommendations

Pharmaceutical and Indication	Recommendation
• Upadacitinib – for the treatment of ankylosing spondylitis (AS) following inadequate benefit from at least one biologic therapy and for the treatment of AS following inadequate benefit from at least two biologic therapies	Cost neutral
• Upadacitinib – for the treatment of psoriatic arthritis (PsA) following inadequate benefit from at least one biologic therapy, and for the treatment of PsA following inadequate benefit from at least two biologic therapies.	Cost neutral
• Tocilizumab for polymyalgia rheumatica	Deferred
• Adalimumab, etanercept, and secukinumab for the treatment of psoriatic arthritis: removal of Special Authority criteria relating to CRP and ESR [P-001735]	High priority
• Adalimumab, etanercept and secukinumab - Psoriatic arthritis - review of SA criteria relating to number of csDMARDs previously trialled [P-001905]	Low priority

3. The role of Specialist Advisory Committees and records of meetings

3.1. This meeting record of the Rheumatology Advisory Committee is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) 2021 and Specialist Advisory Committees 2021.Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of Specialist Advisory Committees and PTAC.

3.2. Conflicts of Interest are described and managed in accordance with section 6.4 of the SAC Terms of Reference.

3.3. The Rheumatology Advisory Committee is a Specialist Advisory Committee of Pharmac. The Rheumatology Advisory Committee and PTAC and other Specialist Advisory Committees have complementary roles, expertise, experience, and perspectives. The Rheumatology Advisory Committee and other Specialist Advisory Committees may therefore, at times, make recommendations for treatments for Rheumatology that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for treatments for Rheumatology that differ from the Rheumatology Advisory Committee's, or Specialist Advisory Committees may make recommendations that differ from other Specialist Advisory Committees'.

Pharmac considers the recommendations provided by both the Rheumatology Advisory Committee and PTAC and any other relevant Specialist Advisory Committees when assessing applications for treatments for Rheumatology.

4. Welcome and introduction

4.1. The Chair welcomed the Committee.

5. Records of previous Rheumatology Advisory Committee meetings

5.1. The Committee noted the records from the Rheumatology Advisory Committee meeting held on 14 May 2021, 18 August 2021, and 31 August 2021.

5.2. The Advisory Committee noted following items that were considered for discussion at a future meeting (noted in the 14 May 2021 record):

5.2.1. The Committee noted that the funding applications for upadacitinib for psoriatic arthritis and for ankylosing spondylitis are to be considered in this meeting. The Committee noted that the funding application for tofacitinib for rheumatoid arthritis has been recommended for funding with a medium priority by both the Rheumatology Advisory Committee in 2017 and PTAC in August 2019, and has been ranked on Pharmac's Options for Investment list. The Committee considered that there are no JAK inhibitors funded in the paediatric setting and that there is therefore an unmet need in this population.

5.2.2. The Committee expressed they would like to review tocilizumab for giant cell arteritis. The Committee noted that Pharmac has not yet received a funding application for this item, however it is expected that a funding application will be submitted in the near future by the supplier.

5.2.3. The Committee noted that Pharmac has not yet received a funding application for IL23 p19 inhibitors for psoriatic arthritis and for ankylosing spondylitis.

5.3. The Advisory Committee reviewed the records of the ad hoc Rheumatology Subcommittee meeting held on 18 August 2021 and agreed that the records be accepted.

5.4. The Advisory Committee reviewed the records of the ad hoc Rheumatology Subcommittee meeting held on 31 August 2021 and agreed that the records be accepted.

6. Correspondence and Matters Arising

Evaluation of the adalimumab brand change implementation process

Discussion

6.1. The Committee noted that in 2021 Pharmac announced the decision to widen access to adalimumab and fund Amgevita, a citrate-free biosimilar adalimumab. The Committee noted that this decision was the result of a competitive procurement process for the Principal Supply of funded adalimumab. The Committee noted that Amgevita became the main funded brand of adalimumab in New Zealand from 1 October 2022 with Principal Supply Status until 31 July 2026.

6.2. The Committee noted that four main workstreams were created to support the implementation for this brand change:

6.2.1. Support for healthcare professionals: The Committee noted that the aim of this workstream was to address confidence in prescribing and supplying biosimilar adalimumab, as well as public perceptions to a brand change. The Committee noted that educational resources on biosimilar medicines and brand changes were covered through Pharmac's Responsible Use of Medicines contract with He Ako Hiringa. The Committee noted that educational resources specifically relating to Amgevita were provided via a suite of Amgen resources, with additional resources provided by He Ako Hiringa.

6.2.2. Support for individuals prescribed adalimumab: The Committee noted that the aim of this workstream was to address challenges with brand loyalty and service availability as well as supporting the healthcare system with the change. The Committee noted that Amgen provided a support package including: a welcome card for people prescribed Amgevita showing how to access support materials; electronic resources on the Amgen website; nursing support available by email, phone, video chat, or in-person; and a sharps bin and alcohol wipes delivery. The Committee noted that only four people requested the in-person nurse support.

6.2.3. Support for the safe prescribing and dispensing of adalimumab: The Committee noted that the aim of this workstream was to support confident prescribing and supplying of a biosimilar, and to direct individuals concerned to the right healthcare professionals at the right time. The Committee noted that this included various support such as automatic issuing of a Special Authority for Amgevita to reduce the risk of treatment interruption. The Committee noted other steps that were taken in this space, which included targeted communications to healthcare professionals, dispensary and prescribing system alerts, texts to individuals taking adalimumab with supportive information, prescribing system alerts to help identify people using Humira, and Brand Switch Fees for pharmacists.

6.2.4. Communication, engagement, and monitoring: The Committee noted that the aim of this workstream was to signal availability of resources, ensure communications are up to date, and provide engagement with key stakeholders. The Committee noted that around 6,800 people currently use Amgevita.

6.3. The Committee noted that Pharmac had reviewed aspects of the implementation process and activities:

6.3.1. Communication to the sector: The Committee noted that Pharmac had planned proactive notifications to stakeholders timed to coincide with Amgen's website go live date, however the website go-live date and hence Pharmac's communications were delayed, leaving very little time between the website go-live date and the date Amgevita was listed. The Committee considered that communication to the sector on the adalimumab brand change occurred too late to allow for prescribers and people taking adalimumab to prepare for this change.

6.3.2. Amgevita Special Authority criteria issuing: The Committee noted that Pharmac arranged for Amgevita Special Authorities to be automatically issued for those taking Humira. The Committee noted that the intention of this arrangement was to ensure people had access to the newly funded alternative of adalimumab, to avoid treatment interruption, and to reduce administrative burden for prescribers. The Committee noted that the automatic approval of Amgevita Special Authorities did not occur as planned for a group of people due to technical problems, which created difficulties for people taking adalimumab and their prescribers. The Committee noted that Pharmac is unlikely to use this process in the future, to prevent this happening again. The Committee noted that from 1 July 2022 Pharmac added an additional criterion to the Amgevita Special Authority criteria for any further individuals who were not automatically issued a Special Authority.

6.3.3. Humira Special Authority criteria: The Committee noted that Pharmac also received feedback that the process would have been more straightforward if people who returned to Humira after a trial of Amgevita did not have their Humira Special Authority cancelled on 1 October 2022.

6.3.4. Impact of COVID-19 on stock levels: The Committee noted that there were issues with delayed adalimumab stock arrival due to the impact of COVID-19 on international supply chains, which should have been predicted and planned to mitigate.

6.3.5. Amgen nursing support program: The Committee considered that there were concerns regarding the in-person nursing support programme offered by Amgen relating to accessibility.

6.4. Members noted other issues experienced during the adalimumab brand change:

6.4.1. Members considered that some individuals were switched prematurely by their pharmacist before rheumatologists had an opportunity to appropriately counsel individuals on the brand change.

6.4.2. Members considered that support for individuals was inadequate due to difficulties accessing the nurse support programme, and educational material that was clinician-focused and not appropriate for use by people taking Amgevita.

6.4.3. Members also noted that supporting resources were not linked into Health Pathways, and considered this would have been beneficial for primary care.

6.4.4. Members also considered that the extension of the Special Authority renewal periods to two years when listing Amgevita has been significantly helpful.

6.5. Members noted that Pharmac staff have reviewed feedback relating to the adalimumab brand change and will ensure they will apply these lessons to implementation plans for future similar brand changes.

7. Upadacitinib and tocilizumab waivers for rituximab for COVID-19 patients with seropositive rheumatoid arthritis

Discussion

7.1. The Committee noted that Pharmac has granted Special Authority waivers for tocilizumab and upadacitinib to waive the requirement to trial rituximab since the outbreak of COVID-19 in New Zealand. The Committee noted that multiple clinicians had expressed concerns that rituximab would put people with rheumatoid arthritis at high risk of serious illness from COVID-19 due its B-cell depleting effects.

7.2. The Committee noted that the purpose of this item was to seek advice on the evidence supporting the on-going granting of Special Authority waivers for upadacitinib and tocilizumab for seropositive rheumatoid arthritis, whereby Pharmac considers waiving the requirement to trial rituximab due to COVID-19 infection risk. The Committee noted the COVID-19 pandemic is now in a different context than it was when upadacitinib and tocilizumab waivers were first approved in October 2021.

7.3. The Committee noted that the following advice was provided via an ad-hoc meeting in October 2021, which supported Pharmac's decision making:

- Rituximab confers an increased risk of severe outcomes from COVID-19;
- It was uncertain how long the risk would last, but was expected to be for 6 to 12 months;
- The risk of COVID-19 from other known risk factors are likely to be independent of the increased risk conferred by rituximab;
- JAK inhibitors overall have an increased risk of severe COVID-19, but which is lower than the risk observed with rituximab;
- The evidence base at the time was of low quality and strength.

7.4. The Committee noted that since the original advice, COVID-19 infection has become more commonplace, high levels of vaccination rates have been achieved (particularly for those at highest risk), the more recent dominant SARS-CoV-2 variants (eg Omicron) generate less acutely severe clinical disease than that of the older variants (ancestral, Delta) which were dominant during 2020-2021, and more evidence has emerged on the risk of COVID-19 conferred by rituximab and other treatments for rheumatoid arthritis.

7.5. The Committee noted that, since 26 October 2021, Pharmac has approved one tocilizumab waiver and 33 upadacitinib waivers by reason of rituximab not being appropriate in the COVID-19 context.

7.6. The Committee noted the following evidence relating to the risk of COVID-19 in people with rheumatoid arthritis using rituximab:

7.6.1. The Committee noted a cohort study of 1090 people with inflammatory arthritis and highly suspected or confirmed COVID-19, in France from April to November 2020. The Committee noted that this study reported a statistically significant higher propensity-adjusted frequency of severe disease and longer hospital stays in the rituximab group compared with no rituximab, but a corresponding increased risk of death was not statistically significant (Avouac et al. Lancet. 2021;3:e419-e426).

7.6.2. The Committee noted a cohort study of 2869 people with rheumatoid arthritis on b/tsDMARDs at the onset of COVID-19, using the COVID-19 Global

Rheumatology Alliance physician registry, cases March 2020 to April 2021. The Committee noted that this study reported that rituximab (odds ratio [OR] 4.15, 95% confidence interval [CI] 3.16 to 5.44) and JAK inhibitors (OR 2.06, 95% CI 1.60 to 2.65) were each associated with worse COVID-19 severity compared with TNF inhibitors, and that there were no associations between abatacept or IL6 inhibitors and COVID-19 severity (Sparks et al. Ann Rheum Dis. 2021;80:1137-46).

7.6.3. The Committee noted a retrospective, national sampled cohort study of 69,549 people with rheumatoid arthritis and COVID-19, using the US National COVID Cohort Collaborative (N3C), COVID-19 cases January 2020 to mid-September 2021. The Committee noted that, compared to csDMARDs, rituximab use was associated with an increased odds of COVID-19 related hospitalisation (adjusted odds ratio [aOR] 2.1, 95% CI 1.5 to 3.0), ICU admission (aOR 5.2, 95% CI 1.8 to 15.4) and invasive ventilation (aOR 2.6, 95% CI 1.4 to 5.5) (Singh et al. Semin Arthritis Rheum. 2023;58:152149).

7.6.4. The Committee noted a cohort study of 2274 people with inflammatory rheumatic and musculoskeletal diseases and COVID-19, using the German COVID-19-RMD registry, COVID-19 cases April 2020 to early April 2021. The Committee noted that, compared with methotrexate, TNF inhibitors had a significant association with better outcome of SARS-CoV-2 infection (OR 0.6, 95% CI 0.4 to 0.9). Immunosuppressants (mycophenolate mofetil, azathioprine, cyclophosphamide and ciclosporin) (OR 2.2, 95% CI 1.3 to 3.9), JAK inhibitors (OR 1.8, 95% CI 1.1 to 2.7) and rituximab (OR 5.4, 95% CI 3.3 to 8.8) were independently associated with worse outcomes (Regierer et al. RMD Open. 2021;7:e001896).

7.6.5. The Committee noted a retrospective cohort study of adults with COVID-19 who had a pre-existing diagnosis of rheumatoid arthritis (n=9730) compared to adults with COVID-19 without rheumatoid arthritis (n=656,979), COVID-19 cases mid-January 2020 to mid-April 2021. The Committee noted that in the patients with rheumatoid arthritis identified with COVID-19 (average age 61.1 years), there were 2334 hospitalisations (24.0% of the 9730 cases), 466 admissions to ICU (4.8%) and 357 deaths (3.7%). The Committee noted that these crude rates were higher than the crude rates for patients without RA (15.0%, 2.6%, 1.7% in the 656,979 patients for hospitalisations, ICU admission and death respectively), noting confounding by age (non-RA patients' mean age was 47.6 years). The Committee noted that the propensity-matched risk of hospitalisation was significantly higher in rituximab or IL-6 inhibitor users compared to TNF inhibitor users, with no significant difference between JAK inhibitor or abatacept users and TNF inhibitor users (Raiker et al. Semin Arthritis Rheum. 2021;51:1057-66).

7.7. The Committee considered that rituximab confers a heightened risk of worse outcomes from COVID-19, including severe illness and death. The Committee considered that tocilizumab and upadacitinib provide equally effective and safer alternatives to rituximab for treatment of rheumatoid arthritis, and that treatment with these agents is therefore preferred. Members considered that this is of particular concern for elderly individuals, and the COVID-19 vaccination is less effective at preventing these risks.

7.8. The Committee considered that the evidence reviewed was consistent. The Committee also noted that most of the studies have not specified the COVID-19 variants prevalent, and that this is likely due to the timing at which these studies were conducted. Members were also made aware of local data encompassing approximately 1600 patients, which reported people treated with rituximab

presenting more frequently to hospital with more severe manifestations of COVID-19, and that this feature is consistent with the experience internationally. The Committee considered that the patterns seen with use of rituximab and worse COVID-19 outcomes may also be relevant for influenza outcomes, however noting that there was no apparent available data supporting this.

7.9. The Committee considered that it would be appropriate to review and consider changes to the treatment paradigm for rheumatoid arthritis to accommodate for the risks associated with rituximab in the COVID-19 setting.

7.10. The Committee considered it would be appropriate for Pharmac staff to initiate a funding application to review the currently Special Authority criteria for upadacitinib and tocilizumab to better reflect the associated risk of rituximab treatment in those with rheumatoid arthritis in the COVID-19 setting. The Committee noted the applications for upadacitinib for moderate to severe rheumatoid arthritis (P-001418 and P-001846) that are currently under assessment would not include criteria requiring a previous trial of rituximab, if these applications were to be funded.

7.11. The Committee considered it appropriate for Pharmac to continue approving applications to waive the criterion requiring people to trial rituximab for tocilizumab and upadacitinib Special Authority criteria until a long-term solution is determined. The Committee considered that it would be difficult to further disaggregate and limit this population, and could not identify a smaller group who would have a comparatively higher risk.

8. Therapeutic Group and NPPA Review

Discussion

General

8.1. The Advisory Committee noted that since its last meeting, PTAC had reviewed a number of funding applications for rheumatological indications. The Advisory Committee noted the record of PTAC's consideration and its recommendations. The Advisory Committee noted PTAC recommendation that several funding applications be reviewed by the Rheumatology Advisory Committee and are therefore to be considered in this meeting, including upadacitinib for second line and third line psoriatic arthritis, and upadacitinib for second line and third line ankylosing spondylitis.

8.2. Members noted that there are limited funding applications for JAK inhibitors for paediatric indications.

NPPA

8.3. The Committee noted the Named Patient Pharmaceutical Assessment (NPPA) applications received since its last meeting. The Committee noted that a large number of applications were withdrawn or had been determined not to meet the principles of NPPA. The Committee noted that the majority of applications where the NPPA principles had not been met were for adalimumab and secukinumab, for indications that have since been approved for funding; there were also several applications for tofacitinib for rheumatoid arthritis and psoriatic arthritis, ustekinumab for psoriatic arthritis, and subcutaneous tocilizumab for those people with both rheumatological conditions and poor venous access.

8.4. Members considered that there is an unmet need for effective treatments for tophaceous gout, and noted that while NPPAs have been approved, rasburicase has limited effectiveness in treating gout. The Committee considered that

pegloticase would be a more effective option, however this is not Medsafe approved. The Committee noted no NPPA applications had been received for pegloticase.

Anti-rheumatoid Agents

8.5. The Committee noted that the overall use of anti-rheumatoid agents has remained relatively stable over the past five years.

8.6. The Committee noted that on 24 March 2020 Pharmac restricted funded access to hydroxychloroquine to ensure it was available for individuals who need it for its registered indications. The Committee noted that this was early in the COVID-19 pandemic, when hydroxychloroquine was suggested internationally as a possible COVID-19 treatment and there were concerns that high demand would jeopardise hydroxychloroquine supplies for people with other conditions. The Committee noted that prescription numbers for hydroxychloroquine have increased slightly since 2020. The Committee considered it appropriate to continue funding hydroxychloroquine under the current funding only with prescription endorsement condition.

Hyperuricaemia and Antigout

8.7. The Committee noted that the overall use of hyperuricaemia and antigout agents has remained relatively stable over the past five years for all agents except allopurinol, where use continues to increase.

8.8. The Committee noted that Pharmac has conducted a series of research insights to implement the Medicine Access Equity Monitoring and Outcomes Framework, the first of which focuses on the prescribing and dispensing of medicines for gout. The Committee noted the key findings of the Gout insights: Impact on Māori and Pacific peoples health: Gout data insights reports. The Committee was also made aware of a New Zealand-based analysis that aimed to understand national trends in hospital admission for a primary diagnosis of gout over the past 10 years and the quality of care for gout received by these patients before and after the admission (Murdoch et al. Intern Med J. 2021:52:2136-42). Members noted that this study concluded that rates of admission for gout were highest in Pacific peoples and in Māori, and that rates of regular allopurinol dispensing overall were low even after people had been admitted with a primary diagnosis of gout.

8.9. The Committee considered there are significant access equity issues in the pharmaceutical treatment of gout. Members considered that the reports noted do not encompass those who experience issues accessing primary care services. Members considered that cost is a significant barrier to access for Māori and Pacific peoples and that funding 6 months' supply and/or enabling pharmacist supply of allopurinol without a prescription may somewhat lessen these barriers. The Committee considered access to primary care is the leading issue and would remain a key driver of gout inequities until resolved.

8.10. The Committee noted that allopurinol and febuxostat users have broadly similar demographic profiles. The Committee noted that of people starting allopurinol and febuxostat treatment between 2019 to 2022; 21% and 15% of individuals starting allopurinol were of Māori and Pacific ethnicity respectively, and 24% and 13% of individuals starting on febuxostat.

8.11. The Committee noted that Pharmac received a funding application in May 2015 from Te Arai Biofarma to widen the access criteria for febuxostat by removing the requirement for probenecid to be trialled prior to accessing febuxostat treatment. The Committee noted that PTAC recommended this application be funded with a medium priority in August 2015, and that the Rheumatology Advisory Committee

(then Subcommittee) recommended changes to the proposed febuxostat Special Authority criteria in October 2015, which were accepted by PTAC in February 2016. The Committee noted that Pharmac have assessed this as an investment proposal and it has subsequently been ranked on the Options for Investment list.

8.12. Members noted that the clinical requirements relating to allopurinol monitoring and its titration are a barrier to effective care due to the monthly blood tests recommended as part of monitoring. The Committee considered that febuxostat is comparatively a more straightforward drug to manage, however regular e monitoring of kidney function is still recommended and there is heightened cardiovascular risk associated with febuxostat compared with allopurinol.

Muscle Relaxants

8.13. The Committee noted that the overall use of muscle relaxants has remained relatively stable over the past five years for all agents except orphenadrine citrate, where there has been a significant increase in use which has stabilised over the past year. The Committee considered that it is not clear what has driven this trend.

8.14. Members noted that agents within this therapeutic group are typically not used for rheumatology indications and therefore proposed removing this group from future rheumatology therapeutic group reviews.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

8.15. The Committee noted that the overall use of NSAIDs agents has remained relatively stable over the past five years for all agents except celecoxib, where use is increasing.

8.16. The Committee noted that Pharmac currently funds seven different NSAIDs on Schedule B of the Pharmaceutical Schedule (ie for community use), each with a variety of strengths and presentations available. The Committee considered that clinicians are likely to have a preferred strength or formulation when prescribing NSAIDs, and that it would therefore be useful to understand geographical prescribing patterns of the different presentations.

8.17. The Committee noted that Pharmac currently funds nine different presentations of diclofenac sodium, including enteric coated tablets, dispersible tablets, long-acting tablets, suppositories, and an injection. The Committee considered that the availability of a variety of strengths of diclofenac is beneficial for adjusting dose according to renal function. The Committee considered that the dispersible preparation provides a suitable alternative for children, elderly, and those who cannot swallow tablets or capsules.

8.18. The Committee considered that NSAIDs are prescribed across a range of specialties, for example mefenamic acid is primarily prescribed for gynaecological indications. Members considered that having just four funded NSAID agents would be sufficient from a rheumatology perspective, and considered that this would include celecoxib, diclofenac, ibuprofen, and naproxen. The Committee however considered that individuals experience differing adverse effects and efficacy from NSAIDs, and it is therefore appropriate to have several funded alternatives.

8.19. The Committee noted that the Gout insights: Impact on Māori report and Pacific peoples health: Gout data insights report identified that, at the time, the prescribing of NSAIDs in people with gout is high, especially for Māori and Pacific peoples.

Topical Agents for Joint and Muscular Pain

8.20. The Committee noted that the only product that falls within this subgroup is capsaicin cream, and that use for this product has increased. The Committee

noted that the 0.025% strength of capsaicin cream is currently funded via Special Authority for those with osteoarthritis. The Committee considered that if this Special Authority criteria were to be removed, it is likely that prescribing numbers would significantly increase and that it therefore remains appropriate to keep this access criteria in place.

8.21. The Committee noted that there is currently a supply issue affecting both Zostrix and Zostrix HP brands of capsaicin cream. The Committee noted that supplier has secured a supply of an alternate brand, Rugby Capsaicin Topical Cream (both strengths have the same name). The Committee noted that these alternatives are listed in the Pharmaceutical Schedule and are not Medsafe approved, and as such need to be prescribed and dispensed in line with Section 29 of the Medicines Act. The Committee considered having different strengths of capsaicin cream with the same name may increase the risk of prescribing and dispensing errors.

Other therapeutic groups of relevance

8.22. The Committee noted that there are several other anti-rheumatoid agents used within rheumatology that are listed in the Pharmaceutical Schedule under other therapeutic groups, including various biological medicines.

8.23. The Committee noted Pharmac's decision in 2021 to widen access to adalimumab and fund Amgevita, a citrate-free biosimilar adalimumab. The Committee noted that the implementation process for this brand change was discussed as a separate agenda item at this meeting.

8.24. The Committee noted the tocilizumab supply shortage which occurred in late 2021 due to significant increase in demand worldwide (due to its increased use in the treatment of severe cases of COVID-19), and the various steps taken by Pharmac to ensure people received the treatment they needed during this time. The Committee noted supply of this medicine has now returned to normal.

Horizon scanning

8.25. Members considered that there is a significant unmet need for treatment options for people with lupus, noting that the current treatment options include hydroxychloroquine, cytotoxic agents, and rituximab. The Committee considered that belimumab would be a beneficial alternative to rituximab in this group. The Committee noted that Pharmac received a funding application in February 2023 for belimumab for lupus nephritis and that this is currently awaiting clinical advice from Pharmac's expert clinical advisors.

8.26. Members considered that there is a need for funded IL-1 inhibitors for use in rheumatological conditions, particularly auto-inflammatory disorders (for example, systemic onset juvenile idiopathic arthritis, cryopyrin associated periodic syndrome, tumour necrosis factor receptor associated periodic syndrome and adult-onset Still's disease). Members considered that there is also an unmet need for JAK inhibitors in the paediatric rheumatological setting, and secukinumab for treatment of juvenile idiopathic arthritis and enthesitis-related arthritis.

8.27. Members considered that there are numerous novel agents that they expect funding applications may be made for in the coming years, including guselkumab, ixekizumab, avacopan and anifrolumab for treatment of a variety rheumatological conditions.

9. Upadacitinib – for the treatment of ankylosing spondylitis (AS) following inadequate benefit from at least one biologic therapy and for the treatment of AS following inadequate benefit from at least two biologic therapies

Application

9.1. The Advisory Committee reviewed the application for upadacitinib for the treatment of ankylosing spondylitis (AS) following inadequate benefit from at least one biologic therapy, and for the treatment of AS following inadequate benefit from at least two biologic therapies.

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

Recommendation

9.3. The Advisory Committee **recommended** that upadacitinib for be for the second-line treatment of AS following inadequate benefit from at least one biologic therapy be listed **only if cost neutral** to secukinumab within the context of rheumatology treatments, subject to the following Special Authority criteria:

> **Initial application — (ankylosing spondylitis – second-line biologic or tsDMARD)** from any relevant practitioner. Approvals valid for 3 months for applications meeting the following criteria:
> Both:
> 1. The patient has had an initial Special Authority approval for adalimumab and/or etanercept for ankylosing spondylitis; and
> 2. Either
>   2.1. The patient has experienced intolerable side effects from adalimumab and/or etanercept; or
>   2.2. Following 12 weeks of adalimumab and/or etanercept treatment, the patient did not meet the renewal criteria for adalimumab and/or etanercept for ankylosing spondylitis.
>
> **Renewal — (ankylosing spondylitis – second-line biologic)** only from a rheumatologist or practitioner on the recommendation of a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Following 12 weeks initial treatment with upadacitinib, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) has improved by 4 or more points from pre-upadacitinib baseline on a 10-point scale, or by 50%, whichever is less; and
> 2. The patient has benefitted from treatment and continued treatment is appropriate; and
> 3. Upadacitinib to be administered at doses no greater than 15 mg daily.

9.4. In making this recommendation, the Committee considered:

9.4.1. The evidence for upadacitinib for AS does not currently show significant treatment benefit over secukinumab

9.4.2. The available evidence for safety of treatments for AS indicates an acceptable safety profile with upadacitinib relative to other treatments

9.4.3. The Committee considered people requiring treatment for AS may prefer upadacitinib due to its suitability advantage of oral administration

9.4.4. That if upadacitinib was funded in a second-line setting, only a small group would receive upadacitinib instead of a second-line anti-TNF, due to the effectiveness and established safety profile of second-line anti-TNFs

9.5. The Advisory Committee **recommended** that upadacitinib for be the third-line treatment of AS following inadequate benefit from at least two biologic therapies be listed with a **medium priority** within the context of rheumatology treatments, subject to the following Special Authority criteria:

Initial application — (ankylosing spondylitis – third-line biologic or tsDMARD) therapy from any relevant practitioner. Approvals valid for 3 months for applications meeting the following criteria:
Both:

1. The patient has had an initial Special Authority approval for secukinumab and/or infliximab for ankylosing spondylitis; and
2. Either
    2.1. The patient has experienced intolerable side effects from secukinumab and/or infliximab; or
    2.2. Following 12 weeks of secukinumab and/or infliximab treatment, the patient's disease did not meet the renewal criteria for secukinumab and/or infliximab for ankylosing spondylitis.

Renewal — (ankylosing spondylitis – third-line biologic or tsDMARD) only from a rheumatologist or practitioner on the recommendation of a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1. Following 12 weeks initial treatment with upadacitinib, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) has improved by either 4 or more points from pre-upadacitinib baseline on a 10-point scale, or by 50%; and
2. The patient has benefitted from treatment and continued treatment is appropriate; and
3. Upadacitinib to be administered at doses no greater than 15 mg daily.

9.6. In making this recommendation, the Committee considered:

9.6.1. that if all aspects (including costs) were equal, then it would be clinically useful to have upadacitinib available after trial of anti-TNF treatment, and alongside secukinumab and infliximab, as per the ASAS-EULAR guidelines.

9.6.2. The available evidence for safety of treatments for AS indicates similar efficacy, and an acceptance safety profile with upadacitinib relative to second line treatment options.

9.6.3. That people requiring treatment for AS may prefer upadacitinib due to its suitability advantage of oral administration.

9.6.4. That upadacitinib would be used for most individuals as a third-line option before infliximab due to suitability and stability advantages.

Discussion

Māori impact

9.7. The Committee discussed the impact of funding upadacitinib for the treatment of AS on Māori health areas of focus and Māori health outcomes. The Committee noted that it was previously recorded that more than 90% of cases of AS are associated with the presence of HLA-B27, which has varying prevalence in different populations and is reported to be less common in Māori (6.5%) than non-Māori (9.2%) (Roberts et al. Arthritis Res Ther. 2013;15:R158). The Committee noted that the current incidence and prevalence of AS in Māori are unknown. The Committee noted that during 2021-2022, 6.9% of individuals with AS who received biologic disease modifying anti-rheumatic drug (bDMARD) treatment were Māori. The Committee considered that there was no direct evidence of a disproportionate impact from AS on Māori.

Background

9.8. The Committee noted that in May 2022, PTAC recommended upadacitinib be listed in the Pharmaceutical Schedule for third-line treatment of AS with a low priority, and that upadacitinib be listed in the Pharmaceutical Schedule for the second-line treatment of AS only if cost-neutral to secukinumab.

9.9. The Committee noted that, at this time, PTAC recommended that Pharmac seek further advice regarding upadacitinib for PsA from the Rheumatology Advisory Committee, including the Committee's views of:

- The sequencing of bDMARD treatments for AS
- The reason for the lower uptake of secukinumab than anticipated for the treatment, and whether there is an existing group of people with AS who would be likely to switch to upadacitinib upon listing
- The appropriate comparator for upadacitinib third-line (ie a second anti-TNF or secukinumab) and what subsequent treatments would be, if upadacitinib were listed third-line for AS
- The Special Authority criteria for upadacitinib for the treatment of AS
- Secukinumab first-line use and whether upadacitinib would be used second-line following first-line secukinumab
- Whether there is a prevalent group of people who would switch to upadacitinib second-line and third-line upon listing and what size that group might be
- The dosing of upadacitinib for the treatment of AS

Health need

9.10. The Committee noted that AS is a chronic condition that occurs in approximately0.25% of the population. The Committee noted that the applicant stated that the prevalence of AS is 0.25% in the adult population, citing evidence for prevalence ranging from 0.1% to 1.4%. The Committee noted that peak symptom onset often occurs between the ages of 20 to 30 years.

9.11. The Committee noted that AS is an incurable, lifelong disease and is associated with significant loss of quality of life, including disability and unemployment. The Committee noted that the inflammation associated with AS may contribute to increased risk of cardiovascular events. The Committee noted that retrospective evidence indicates that AS may be linked with increased mortality (Ben-Shabat et al. Arthritis Care Res (Hoboken). 2022;74(10):1614-22; Chaudhary et al. Arthritis Care Res (Hoboken). 2021;17).

9.12. The Committee considered that the families and whānau of people with AS were also impacted, and had an unmet health need with the loss of employment and family impact associated with AS.

9.13. The Committee noted the impact of funding upadacitinib for the treatment of AS on Māori health areas of focus and Māori health outcomes. The Committee noted that it was previously recorded that more than 90% of cases of AS are associated with the presence of HLA-B27, which has varying prevalence in different populations and is reported to be less common in Māori (6.5%) than non-Māori (9.2%) (Roberts et al. Arthritis Res Ther. 2013;15:R158). An audit conducted in the Wellington/Southern regions across 10 years reported 23% of cases occurred in European people, and 17% in Māori. The Committee noted that the current incidence and prevalence of AS in Māori are unknown. The Committee noted that during 2021-2022, 6.9% of individuals with AS who received bDMARD treatment were Māori, and 2.1% were of Pacific ethnicity.

9.14. The Committee noted that non radiographic axial spondyloarthritis is a similar disease to radiographic axial spondyloarthritis (AS) with similar disease burden and treatment, however is important to differentiate when appraising evidence.

9.15. The Committee considered that anti-TNF bDMARDS are generally effective in treating AS, and that there was clinician comfort and familiarity with anti-TNFs in

this setting. The Committee considered that because of the effectiveness of anti-TNFs in this setting, it was relatively common for people to switch to a second anti-TNF after loss of response to the first anti-TNF, rather than switching out of class. The Committee considered that those who experience no response to the first anti-TNF may switch out of class to secukinumab as a second-line biologic therapeutic, rather than switching to a second anti-TNF. The Committee considered that most individuals would trial a second anti-TNF therapy before trialling secukinumab. The Committee considered that there was also likely to be a small group of individuals who would receive a second anti-TNF after trialling second-line secukinumab treatment.

Health benefit

9.16. The Committee noted that upadacitinib is an oral, reversible inhibitor of Janus Kinase-1 (JAK1). The Committee noted that JAK1 is important in inflammatory cytokine signals and has a role in the pathogenesis of spondyloarthritis, so administration of a JAK1 inhibitor leads to decreased inflammation.

9.17. The Committee noted that the recommended dose of upadacitinib for AS is one 15 mg modified release table once daily by mouth taken with or without food.

9.18. The Committee noted the following evidence, which was reviewed by PTAC in May 2022: The Committee noted the following clinical measurements commonly used in studies relating to AS:

9.18.1. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), a patient-reported assessment of disease activity and symptom severity which uses scales from zero to ten.

9.18.2. The Bath Ankylosing Spondylitis Functional Index (BASFI), a patient-reported assessment of difficulty with daily activities which uses a scale from zero to ten and is routinely used in secondary care.

9.18.3. The Assessment in Ankylosing Spondylitis (ASAS) response criteria, which require either a 20%, 40%, 50% or 70% improvement (ASAS20/40/50/70) and an absolute improvement of at least 10 units on a 0-100 scale in at least three of the following domains: patient global assessment, pain assessment, function (BASFI), and inflammation (last two questions of BASDAI).

9.19. The Committee noted that the key evidence for upadacitinib in AS comes from SELECT AXIS 2, a phase III, multicentre, randomised, double-blind, placebo-controlled study that included 420 adult participants with active AS who had BASDAI score of four or greater and who received an inadequate response from or experienced intolerance to one or more bDMARDs (bDMARD-IR AS). The Committee noted that, of these 420 participants, 206 (98%) on upadacitinib and 203 (97%) on placebo completed the 14-week double-blind treatment period. The Committee noted that the primary endpoint was Assessment of SpondyloArthritis international Society 40 (ASAS40) response at week 14.

9.20. The Committee noted that a higher proportion of participants in SELECT-AXIS 2 experienced the primary endpoint of ASAS40 at week 14 in the upadacitinib group vs the placebo group (45% vs 18%; *P*=<0.0001) with a treatment difference of 26% (95% CI 18% to 35%) (Heijde et al. Ann Rheum Dis. 2022;81(11):1515-23). The Committee noted that greater ASAS40 treatment effects were also seen with upadacitinib vs placebo in the subgroups of participants treated with one (46% vs 20%) or two (36% vs 4%) prior bDMARDs, and that improvements in disease activity, function and pain were achieved among upadacitinib-treated vs placebo-treated patients at week 14, (*P*=<0.0001).

9.21. The Committee also noted evidence from SELECT-AXIS 1, which examined upadacitinib in the first line vs placebo in patients with advanced AS who have received an inadequate response from at least one DMARD. The Committed noted PTAC's considerations in May 2022, and added that at the 2-year open label extension had been published and showed among patients receiving continuous upadacitinib, 85.9% using as observed and 65.6% non-responder imputation achieved ASAS40 at week 104 (Van der Heijde. RMD Open. 2022;8(2):e002280).

9.22. The Committee noted that Australia's PBAC recommended listing upadacitinib for adults with AS following experiencing inadequate response to at least two NSAIDs combined with an exercise program (as a first-line biologic). The Committee noted Scotland's SMC recommended the use of upadacitinib for the treatment of active AS in adult patients whose disease has responded inadequately to conventional therapy, and England/Wales' NICE recommended upadacitinib as an option for treating active AS that is not controlled well enough with conventional therapy in adults when TNF-alpha inhibitors are not suitable or do not control the condition well enough, and the company provide upadacitinib according to the commercial arrangement.

9.23. The Committee noted that the 2022 update of the Assessment of Spondyloarthritis international Society (ASAS)-EULAR recommendations for the management of axial spondyloarthritis recommends that following a first bDMARD failure, switching to another bDMARD (Anti-TNFr or IL-17 inhibitor) or a JAK inhibitor should be considered and that upadacitinib, as a JAK inhibitor fits within this group.

9.24. The Committee noted the following publications reviewed by PTAC in May 2022:

- Zhou et al. Mediators Inflamm. 2020;2020:1639016
- M19-944 Clinical Study Report – Week 14 Study 1 (bDMARD-IR AS)
- Baeten et al. N Engl J Med. 2015;373:2534-48
- Sieper et al. Ann Rheum Dis. 2017;76:571-92
- Marzo-Ortega et al.Arthritis Care Res. 2017;6:1020-9
- Marzo-Ortega et al. RMD Open. 2017;3:e000592
- Marzo-Ortega et al. Lancet Rheum. 2020; 2:E339-46
- Kivitz et al. Rheumatol Ther. 2018;5:447-62

9.25. The Committee considered the quality of evidence for efficacy of upadacitinib in treating AS was high.

9.26. The Committee considered that the evidence above suggested that upadacitinib is effective for the treatment of AS. The Committee considered that assuming there is broad equivalence of efficacy across bDMARDS, sequencing should be driven by financial impact, as there is limited direct comparison data available. The Committee considered that it was reasonable to assume, based on the evidence available, that upadacitinib has similar efficacy to secukinumab.

9.27. The Committee considered that upadacitinib would be used for most individuals as a third-line option before infliximab due to suitability and stability advantages. The Committee considered that there may still be a small number of individuals who would use infliximab instead of upadacitinib due to the effectiveness of anti-TNF treatment. The Committee considered that upadacitinib does not provide sufficient clinical benefit to be used ahead of secukinumab for most people.

9.28. The Committee considered that the treatment paradigm for AS should be tailored to each individual. The Committee considered that if all aspects (including costs) were equal, then it would be clinically useful to have upadacitinib available after trial of anti-TNF treatment, and alongside secukinumab and infliximab, as per the ASAS-EULAR guidelines.

Suitability

9.29. The Committee noted that upadacitinib is an oral treatment which can be self-administered at home, and that in comparison, secukinumab is given as a subcutaneous injection in either a primary or secondary care clinic with monthly dosing after the initial dosing period.

9.30. The Committee considered people requiring treatment for AS may prefer upadacitinib due to its oral administration.

Cost and savings

9.31. The Committee considered that if upadacitinib was funded in a second-line setting, only a small group would receive upadacitinib instead of a second-line anti-TNF, due to the effectiveness of second-line anti-TNFs. The Committee considered that if listed second-line, upadacitinib may still be used third line after secukinumab in a group of people, due to the effectiveness of and familiarity with secukinumab.

9.32. The Committee considered that lower than expected uptake of secukinumab may be attributed to the generally good effectiveness of anti-TNFs in AS, which results in the proportion of those with AS who required an additional treatment being relatively low. The Committee considered that AS is also associated with slow progression of disease, and individuals may not have seen their rheumatologist since the funding of secukinumab. The Committee considered more accurate data on secukinumab uptake may be available in 2-3 years. The Committee considered that it seemed plausible that uptake for upadacitinib in this setting would be similar to the uptake observed for secukinumab in AS, or potentially slightly higher given upadacitinib's suitability advantages.

Summary for assessment

9.33. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for upadacitinib if it was funded for ankylosing spondylitis. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with AS who have received inadequate benefit from one prior biologic therapy	People with AS who have received inadequate benefit from second-line secukinumab and/or infliximab
Intervention	Upadacitinib, 15mg daily	
Comparator(s)	Secukinumab for most people, with smaller numbers of individuals otherwise receiving second-line anti-TNFs	Mixture of no biologic treatment, infliximab and a second anti-TNF

Outcome(s)	Similar therapeutic benefit to second-line secukinumab Upadacitinib offers an additional line of treatment, which is associated with greater duration on AS treatment overall and therefore a health benefit compared to best supportive care	Improved signs and symptoms of disease compared to best supportive care
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.		

10. Upadacitinib – for the treatment of psoriatic arthritis (PsA) following inadequate benefit from at least one biologic therapy, and for the treatment of PsA following inadequate benefit from at least two biologic therapies.

Application

10.1. The Advisory Committee reviewed the application for upadacitinib for the treatment of psoriatic arthritis (PsA) following inadequate benefit from at least one biologic therapy for psoriatic arthritis (adalimumab, etanercept, secukinumab, or infliximab), and for the treatment of PsA following inadequate benefit from at least two biologics therapies for psoriatic arthritis.

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

Recommendation

10.3. The Advisory Committee **recommended** that upadacitinib for be for the second-line treatment of psoriatic arthritis (PsA) following inadequate benefit from at least one biologic therapy be listed **only if cost neutral** to secukinumab, subject to the following Special Authority criteria:

Initial application — (psoriatic arthritis – second-line biologic or tsDMARD) only from a rheumatologist **or practitioner on the recommendation of a rheumatologist**. Approvals valid for 6 months for applications meeting the following criteria:
Both:

1. The patient has had an initial Special Authority approval for adalimumab **and/**or etanercept for psoriatic arthritis; and
2. Either
    2.1. The patient has experienced intolerable side effects from adalimumab **and/**or etanercept **and/or secukinumab**; or
    2.2. The patient has received insufficient benefit from adalimumab or etanercept to meet the renewal criteria for adalimumab or etanercept for psoriatic arthritis.

Renewal — (psoriatic arthritis – second-line biologic or tsDMARD) only from a rheumatologist or practitioner on the recommendation of a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1. Either:
    1.1. Following 3 to 4 months' initial treatment, the patient has at least a 50% decrease in active joint count from baseline and a clinically significant response to treatment in the opinion of the physician; or
    1.2. The patient demonstrates at least a continuing 30% improvement in active joint count from baseline or a clinically significant response to prior upadacitinib treatment in the opinion of the treating physician; and
2. Upadacitinib to be administered at doses no greater than 15 mg **daily**.

10.4. In making this recommendation, the Advisory Committee considered:

10.4.1. That assuming there is broad equivalence of efficacy across biological disease modifying anti-rheumatic drugs (bDMARDS), sequencing should be driven by financial impact.

10.4.2. The indirect evidence of benefit from upadacitinib for PsA, which suggests this is similar to that from secukinumab for PsA.

10.4.3. The suitability of an oral treatment for PsA, including the potential impact this formulation may have on health outcomes.

10.5. The Advisory Committee **recommended** that Upadacitinib for the third-line treatment of PsA following inadequate benefit from at least two biologic therapies be listed with a high priority within the context of rheumatology treatments, subject to the following Special Authority criteria:

Initial application — (psoriatic arthritis – third-line biologic therapy) from any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:
Both:
1. The patient has had an initial Special Authority approval for at least two biologic therapies for psoriatic arthritis (adalimumab, etanercept, secukinumab, and/or infliximab); and
2. Either

1.1. The patient has experienced intolerable side effects from prior biologic therapy for PsA; or
1.2. The patient has received insufficient benefit to meet the renewal criteria for prior biologic therapies for psoriatic arthritis.

Renewal — (psoriatic arthritis – third-line biologic therapy) only from a rheumatologist or practitioner on the recommendation of a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. Either:

1.3. Following 3 to 4 months' initial treatment, the patient has experienced at least a 50% decrease in active joint count from baseline or a clinically significant response to treatment in the opinion of the physician; or
1.4. The patient experiences both:
- 1.4.1. at least a continuing 30% improvement in active joint count from baseline and
- 1.4.2. a clinically significant response to prior upadacitinib treatment in the opinion of the treating physician; and

10.6. In making this recommendation, the Advisory Committee considered:

10.6.1. That people may choose to transition from one bDMARD to another (second- or third-line) treatment for various reasons such as the treatment not providing sufficient benefit from the outset, or benefit fading over time, differential skin and joint effects, or intolerable side effects.

10.6.2. That assuming there is broad equivalence of efficacy across bDMARDS, their sequencing should be driven by financial impact, and that based on the evidence available, upadacitinib appeared to be associated with broadly similar efficacy compared to other bDMARDS used in this indication

10.6.3. That as more bDMARDs become available, it will become less likely that individuals with PsA will stay on a bDMARD in the absence of receiving any significant treatment benefit.

10.6.4. The suitability of an oral treatment for PsA, including the potential impact this formulation may have on health outcomes.

Discussion

Māori impact

10.7. The Committee discussed the impact of funding upadacitinib for the treatment of PsA on Māori health areas of focus and Māori health outcomes. Analysis of the

ethnicity of people receiving biologic treatment for PsA across the 2020 and 2021 financial years suggested that 7.6% of those receiving biologics for PsA were Māori. The Committee considered that there was no specific evidence of a disproportionate impact from PsA on Māori.

Background

10.8. The Committee noted that in May 2022 PTAC recommended upadacitinib be listed in the Pharmaceutical Schedule for third-line treatment of PsA with a high priority, and that upadacitinib be listed in the Pharmaceutical Schedule for the second-line treatment of PsA only if cost-neutral to secukinumab. The Committee noted that, at this time, PTAC recommended that Pharmac seek further advice regarding upadacitinib for PsA from the Rheumatology Advisory Committee, including the Committee's views of:

- The sequencing of bDMARD treatments for PsA.
- Whether or not individuals with PsA who receive smaller benefits from treatment (eg a 20% improvement) would remain on their treatment.
- The benefits and risks of second line versus third line use of upadacitinib for PsA and where upadacitinib would be used in the treatment paradigm, if funded.
- The appropriate comparator for upadacitinib third-line use, if funded.
- Secukinumab first-line use and whether upadacitinib would be used second line following first-line secukinumab.
- Whether there is a prevalent group of people who would switch to upadacitinib second-line and third-line upon listing and what size that group might be.
- The Special Authority criteria for upadacitinib for second-line and third-line treatment of PsA.

Health need

10.9. The Committee noted that psoriasis is a common skin disease occurring in 1-3% of the population. PsA is a heterogenous inflammatory musculoskeletal disease which occurs in about 20-30% of people with psoriasis (Fitzgerald et al. Nat Rev Dis Primers. 2021;7:59; Karmacharya et al. Best Pract Res Clin Rheumatol. 2021;35:101692). The Committee noted that it is possible to be classified as having PsA, without meeting the diagnostic criteria for psoriasis. The Committee noted that PsA most frequently presents as polyarthritis, involving peripheral and/or axial joints. The Committee considered that the clinical manifestations of PsA are highly variable and can change over time as the disease progresses.

10.10. The Committee considered that, in terms of disease severity, there are different groups of individuals affected by PsA: some, who experience mild disease symptoms over a long period of time; others who experience consistently severe PsA symptoms, and a further group of people whose symptoms fall between those associated with mild and severe disease. The Committee noted that there is limited data on the longitudinal course of PsA in the New Zealand population.

10.11. The Committee noted that PsA is one of several closely related inflammatory conditions that are collectively grouped under the term spondyloarthritis; this group also includes ankylosing spondylitis, acute anterior uveitis, psoriasis, and inflammatory bowel disease. The Committee considered that PsA is also related to metabolic syndrome and its components including obesity and hypertension (Haroon et al. J Rheumatol. 2014;41:1357-65; Haroon et al. J Rheumatol. 2016;43:463-4).

10.12. The Committee noted that as of September 2021, there were 860 people with PsA in New Zealand who were prescribed a bDMARD for PsA, and that prescribing of bDMARDs is growing annually. The Committee noted that people may choose to transition from one bDMARD to another (second- or third- line) treatment for various reasons such as the treatment not providing sufficient benefit from the outset, or benefit fading over time, differential skin and joint effects, or intolerable side effects. The Committee considered that as more bDMARDs become available, it becomes less likely that individuals with PsA will stay on a bDMARD in the absence of receiving any significant treatment benefit.

Health benefit

10.13. The Committee considered that individuals included in clinical trials presented with severe and mostly homogenous clinical manifestations of PsA, particularly peripheral polyarthritis .

10.14. The Committee considered that, assuming there is broad equivalence of efficacy across bDMARDS, their sequencing should be driven by financial impact. The Committee considered that based on the evidence available, upadacitinib appeared to be associated with broadly similar efficacy compared to other bDMARDS used in this indication, specifically secukinumab, adalimumab, and etanercept.

10.15. The Committee considered that the goal of treatment is typically to attain low disease activity. The Committee considered that persistence on treatment is often determined by personal preferences, and that people may stay on treatment despite receiving smaller benefits from treatment if they feel they are still experiencing improvement.

10.16. The Committee considered that most people would receive first-line treatment with an anti-TNF. The Committee noted Pharmac staff's estimate that approximately 20% of people receive secukinumab as a first-line biologic and considered that this was plausible. The Committee considered that secukinumab would be considered earlier in the treatment algorithm for those people who had severe skin involvement, given secukinumab is associated with better effectiveness in psoriasis. The Committee considered that upadacitinib is also relatively effective for treating skin involvement and so it may be used similarly to secukinumab in those with severe skin involvement.

10.17. The Committee considered that anti-TNFs are less effective in PsA compared to ankylosing spondylitis and considered that secukinumab is used as a second-line biologic more often in PsA than in ankylosing spondylitis, where anti-TNFs are generally more effective than in PsA. The Committee considered that switching to a second anti-TNF after failure of a first anti-TNF is still relatively common in PsA. The Committee considered that secukinumab is often used after trialling two prior anti-TNFs (ie as a third-line option).

10.18. The Committee noted the results of SELECT-PsA; a phase III, randomised, double-blind 1 trial in 1705 patients with active PsA who had a history of inadequate response to at least one conventional synthetic DMARD. The Committee noted that patients were randomised to receive upadacitinib 15 mg or 30 mg once daily, placebo followed by upadacitinib 15 mg or 30 mg once daily starting at week 24, or adalimumab 40 mg every other week. The Committee noted that the primary endpoint of SELECT-PsA 1 was American College off Rheumatology 20 score (ACR20) and was made aware of published 24-week data reporting non-inferiority of upadacitinib 15 mg to adalimumab every other week and a similar higher incidence of infections with upadacitinib 15 mg vs placebo or adalimumab (McInnes et al. N Engl J Med. 2021;384:1227-39).

10.19. The Committee considered this evidence, alongside the recommendation from NICE in February 2022, suggests that the ACR20 response with upadacitinib for PsA in the first-line is slightly better than the response in a second or subsequent line. In February 2022 the NICE recommended upadacitinib for patients with PsA who have had two conventional DMARDs and at least one bDMARD, or for whom anti TNFs are contraindicated due to evidence that upadacitinib is more effective than placebo for treating PsA and may be similarly as effective as adalimumab.

10.20. The Committee considered the results of a post hoc analysis of the SELECT-PsA 1 and 2 trials where 1386 patients were analysed. The Committee noted that disease control was achieved at 24 weeks in upadacitinib treated patients across both studies. The Committee noted that low or minimal disease activity was achieved in 25-48% of patients receiving upadacitinib 15 mg versus 2-16% of patients receiving placebo, and remission or very low disease activity rates were 7-14% with upadacitinib 15 mg versus 0-4% with placebo.

10.21. The Committee noted the following evidence reviewed by PTAC in May 2022:

- Mease et al. Ann Rheum Dis. 2020;80:312-20
- Mease et al. Rheumatol Ther. 2021;8:903-19
- McInnes et al. Lancet. 2015;386:1137-46
- McInnes et al. Rheumatology (Oxford). 2017;56):1993-2003
- McInnes et al. Lancet. 2020;2:E227-35
- Nash et al. Arthritis Res Ther. 2018;20:47
- Mease et al. Ann Rheum Dis. 2018;77:890-7
- van der Heijde et al. Rheumatology (Oxford). 2020;59:1325-34
- Mease et al. RMD Open. 2021;7:e001600

10.22. The Committee noted the published results of the EXCEED trial, which reported secukinumab 300 mg was non-inferior to adalimumab 40 mg as first-line therapy in PsA (McInnes et al. 2020); and noted the evidence for secukinumab in PsA at various doses from several randomised, phase III, placebo-controlled trials:

- FUTURE-2: McInnes et al. Lancet. 2015;386:1137-46; McInnes et al. Rheumatology (Oxford). 2017;56):1993-2003; McInnes et al. Lancet. 2020;2:E227-35
- FUTURE-3: Nash et al. Arthritis Res Ther. 2018;20:47
- FUTURE-5: Mease et al. Ann Rheum Dis. 2018;77:890-7; van der Heijde et al. Rheumatology (Oxford). 2020;59:1325-34; Mease et al. RMD Open. 2021;7:e001600

10.23. The Committee considered the quality of the evidence for the efficacy of upadacitinib for PsA to be high.

Suitability

10.24. The Committee considered that an orally administered biologic therapy would likely be preferred by many people over other formulations, including those who currently have to travel for the administration of other biologic therapies (if they are unable to administer these by self-injection).

Cost and savings

10.25. The Committee considered that positive consequences in the healthcare system from funding upadacitinib for PsA could include a reduction in the time needed to be spent for education and responding to questions about injections, a reduction

expenditure on the sharps disposal service, and the elimination of cold-chain delivery problems.

10.26. The Committee considered that there was a greater need for second line upadacitinib in PsA than in ankylosing spondylitis, and that it was likely that it would be used relatively often in a second-line setting, if available. The Committee considered that upadacitinib would likely displace secukinumab in a relatively large number of patients.

10.27. The Committee noted that secukinumab uptake was higher for PsA than for ankylosing spondylitis, and that this was likely due to a greater proportion of individuals with PsA not deriving optimal disease response from other treatments when compared with the experience of individuals with ankylosing spondylitis. The Committee considered that it was plausible that the pattern of uptake for upadacitinib if funded would likely to be similar to that observed for secukinumab for PsA, or potentially higher.

Funding criteria

10.28. The Committee considered that Special Authority criteria for upadacitinib for PsA should take into account that people with PsA have a mixture of skin and joint health needs, as well as extra articular disease associations including IBD and the consequences of metabolic syndrome.

10.29. The Committee considered that it was reasonable that if listed third-line, that upadacitinib be restricted to use after both an anti-TNF and an IL-17 inhibitor. The Committee considered that there is a small group of people who would receive a second anti-TNF after previously having received both a first-line anti-TNF and secukinumab.

11. Tocilizumab for polymyalgia rheumatica

Application

11.1. The Committee reviewed the application for tocilizumab for the treatment of polymyalgia rheumatica (PMR).

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

Recommendation

11.3. The Advisory Committee **recommended** that tocilizumab for PMR **be deferred**.

11.4. In making this recommendation, the Advisory Committee considered:

11.4.1. It was unclear from the available evidence how long individuals with PMR should be treated with tocilizumab, and further evidence was needed to define:

- the intended population to treat (specifically if this is people experiencing inadequate prednisone effect, people whose PMR has high prednisone dose /duration requirements, or all people with PMR)
- intended treatment duration,
- appropriate timing of when to start treatment.

11.4.2. The health benefit of tocilizumab for PMR would be best derived from reducing the long-term consequences of glucocorticoid treatment including those related to infection, cardiovascular disease, diabetes, and

osteoporosis. Further evidence was required to quantify the impact of these long-term effects.

Discussion

Māori impact

11.5. The Committee discussed the impact of funding tocilizumab for the treatment of PMR on Māori health areas of focus and Māori health outcomes. The Committee noted that there was no available data detailing the rates of PMR in Māori, but considered it was important to note that many Māori have some European and Scandinavian ancestry (ie populations in which the condition is more common). The Committee noted that most of the comorbidities associated with prednisone use inequitably affect Māori, and thus considered that this should be taken into account when assessing alternative therapies such as tocilizumab.

Background

11.6. The Committee noted that Pharmac has not considered any other therapies for the treatment of PMR.

11.7. The Committee noted that tocilizumab is currently funded for the treatment of cytokine release syndrome, rheumatoid arthritis, juvenile idiopathic arthritis (systemic and polyarticular), adult-onset Still's disease, idiopathic multicentric Castleman's disease, and moderate to severe COVID-19 infection.

11.8. The Committee noted that the application specifically applied for tocilizumab to be funded for "polymyalgia rheumatica when response to prednisone dose greater than 5 mg per day has been insufficient and steroid-sparing therapy using methotrexate and leflunomide has failed".

Health need

11.9. The Committee noted that PMR is an inflammatory, rheumatological syndrome that causes pain and stiffness, most commonly in the neck, shoulders, and pelvic girdle (Best Practice Journal [BPAC]. 2013;53:24-31). The Committee considered that when a person experiences the symptoms of PMR, the impact of those symptoms can be severe, including high levels of pain, disability, loss of function and independence.

11.10. The Committee considered that PMR almost exclusively occurs after the age of 50 years, and that the lifetime risk of developing PMR is 2.4% for women and 1.7% for men (Buttgeriet et al. JAMA. 2016;315(22):2442–58). The Committee considered that PMR affects people of all ethnicities, however noted that it is more common in people with European and Scandinavian ancestry. The Committee noted that there was no available data detailing the rates of PMR in Māori, but considered it was important to note that many Māori have some European and Scandinavian ancestry.

11.11. The Committee noted that first line management of PMR is treatment with glucocorticoids, specifically prednisone in New Zealand. The Committee considered that for most individuals, their symptoms respond well to prednisone. The Committee noted that good symptom response often occurs at lower doses of prednisone for treatment of PMR than the doses that are often needed to treat other rheumatological indications. The Committee considered that a strong symptom improvement in response to treatment with prednisone is sometimes a diagnostic factor for PMR.

11.12. The Committee considered that although PMR symptoms tend to respond well to treatment with prednisone, that small decreases in the prednisone dose (as small as 0.5 mg daily) can bring PMR out of remission and lead to a flare of symptoms.

The Committee considered that when symptom flares occur, the standard treatment in New Zealand is to increase the prednisone dose by small increments, gradually increasing the dose until symptom remission is achieved.

11.13. The Committee noted second line treatment for PMR is methotrexate, and that this is in line with The British Society of Rheumatology (BSR) recommendations; that after two relapses, consideration should be given to a trial of disease-modifying, anti-rheumatic drugs (DMARDs), usually methotrexate, despite the weak evidence base (Dasgupta et al. Rheumatology.2010;49:186-90). The Committee noted that methotrexate is usually continued until the dose of glucocorticoids can be tapered down without the recurrence of PMR symptoms. The Committee noted that, once this has successfully occurred, the dose of methotrexate can then also usually be tapered down over approximately three months. The Committee noted that there was some evidence for using leflunomide or azathioprine second line, but that their use was not recommended in the BSR guidelines.

11.14. The Committee considered that the prognosis for individuals with PMR is usually good and complications, such as recurrent, or ongoing, relapses of symptoms, are limited.

11.15. The Committee noted morbidity in PMR most often relates to the longer-term impact of its treatment (ie glucocorticoids) (Salvarani et al. UpToDate. 2022). The Committee noted that prednisone has a negative long-term effect on, and risks developing comorbid conditions such as diabetes, heart disease, and osteoporosis, as well as the risk of infection. The Committee noted that most of the comorbidities associated with prednisone use inequitably affect Māori (eg diabetes, cardiovascular disease, infections), and considered that this should be taken into account when assessing alternative therapies such as tocilizumab.

11.16. The Committee considered there would likely be much higher need to fund agents such as tocilizumab for the treatment of giant cell arteritis, a closely related disease with serious health impacts including blindness.

Health benefit

11.17. The Committee noted that in several randomised controlled trials considered, treatment with tocilizumab was initiated at diagnosis or in the early stages of PMR. The Committee considered that this treatment paradigm was different to guidelines and New Zealand practice, where prednisone is always utilised first line.

11.18. The Committee considered that second line therapies (including tocilizumab) are introduced when prescribers or people receiving treatment consider the adverse effects and co-morbidities associated with prednisone to be unacceptably harmful.

11.19. The Committee noted the following evidence relating to the use of tocilizumab for PMR:

11.20. The Committee noted the results of a double blind, parallel group, placebo controlled, randomised controlled trial conducted in glucocorticoid dependent individuals diagnosed with PMR. The Committee noted that participants were randomised to receive intravenous tocilizumab 8 mg/kg (n=51) or placebo (n=50) every 4 weeks for 24 weeks. The Committee noted that the composite primary endpoint was CRP <10, and either prednisone dosage ≤5 mg/day or prednisone dosage decreased by ≥ 10mg vs baseline at 24-week follow up. The Committee noted that the primary endpoint occurred in 67.3% of participants treated with tocilizumab and 31.4% of participants treated with placebo (adjusted difference, 36.0% [95% CI 19.4% to 2.6%]; adjusted relative risk, 2.3 [95%CI 1.5 to 3.6]; P< .001) (Devauchelle-Pensec et al. JAMA. 2022;20;328(11):1053-62).

11.21. The Committee noted the results of a double blind, multicentre, phase II/III clinical trial conducted in individuals with new onset PMR. The Committee noted that the trial included 19 individuals treated with tocilizumab subcutaneous injection 162 mg/week and 17 individuals treated with placebo for 16 weeks. The Committee noted that all patients received oral prednisone tapered from 20 mg to 0 mg daily over 11 weeks. The Committee noted that the primary endpoint was the proportion of patients in glucocorticoid free remission at week 16, which was achieved in 63.2% (12/19) of the tocilizumab group and 11.8% (2/17) of the placebo group (*P*=0.002, OR 12.9, 95% CI 2.2 to 73.6), and maintained in 91.7% (11/12) patients in tocilizumab group over 8 weeks blinded follow up until week 24 (Bonelli et al. Ann Rheum Dis. 2022;81(6):838-44).

11.22. The Committee noted the results of a single centre, prospective, open-label, phase IIa study conducted in individuals with new onset PMR. The Committee noted that the trial included 10 individuals treated with tocilizumab 8 mg/kg monthly for one year, with rapid glucocorticoid tapering. The Committee noted that the primary endpoint of relapse-free remission without glucocorticoid treatment at 6 months was reached in all 9 individuals in whom the primary endpoint assessed. The Committee noted that disease remained in remission throughout the trial in all 9 patients who completed the entire 15-month trial. The Committee noted that a cohort of 10 consecutively evaluated patients with newly diagnosed PMR served as a comparator group, and that none of this group were in remission without glucocorticoids by 6 months; remission or low disease activity was observed in all 10 patients, but they were all still receiving low-dose glucocorticoids (Lally et al. Arthritis Rheumatol. 2016;68(10):2550-2554).

11.23. The Committee noted the results of a prospective, open label, longitudinal study, conducted in 20 glucocorticoid-free individuals with PMR symptom onset within the previous 12 months and a PMR activity score (PMR-AS) >10. The Committee noted that individuals were given tocilizumab 8 mg/kg via three IV infusions at baseline, week 4, and week 8, followed by oral prednisone 0.15 mg/kg daily from weeks 12 to 24. The Committee noted that the primary endpoint was the proportion of patients with PMR-AS ≤10 at week 12. The Committee noted that at week 12, all patients had PMR-AS ≤10 and received low-dose prednisone, median starting dosage was 12 mg (interquartile range [IQR] 9.0 to 12.5). The Committee noted that at weeks 12 and 24 median PMR-AS improved from 4.50 (IQR 3.2 to 6.8) to 0.95 (IQR 0.4 to 2.0).. The Committee noted that the at week 24, only four patients were still on prednisone therapy, with the median daily prednisone dosage being zero, and that the glucocorticoid-sparing effect of tocilizumab was 70.2% after six months. (Devauchelle-Pensec et al. Ann Rheum Dis. 2016;75(8):1506-10).

11.24. The Committee noted the results of a prospective, single centre, open label pilot study conducted in 13 individuals with PMR. The Committee noted that participants received 8 mg/kg tocilizumab monotherapy administered via fortnightly IV infusion for the first 2 months, then monthly for the next 10 months and then observed for a second year without any treatment. The Committee noted that the primary endpoints were remission rates at weeks 12 and 52, and that at weeks 12, 4 patients achieved remission (remission rate 31%), with all 9 patients who completed the study achieving remission by week 52 (remission rate 69%) (Chino et al. Int J Rheum Dis. 2019;22(12):2151-7). The Committee considered that this study, while open label, showed a long-term benefit after treatment with TCZ for 12 months. The committee noted that the greatest exposure and the highest impact of prednisone is in the first 12 months of treatment. The Committee considered that based on the data from this study, a period of treatment of 12 months could be considered.

11.25. The Committee considered that a reduction in CRP from tocilizumab was to be expected given the mechanism of action of the drug, and it does not necessarily reflect tocilizumab having a clinically meaningful effect.

11.26. The Committee considered that the strength and quality of the evidence for tocilizumab in PMR was mixed, with the randomised controlled trials being of stronger quality than the open label trials. The Committee considered that further evidence was required to assess the benefit of different dosing regimens for tocilizumab in PMR, as the optimal dosing regimen was currently unclear.

11.27. The Committee considered that the health benefit of tocilizumab in this indication would be most derived from reducing the long-term consequences of glucocorticoid treatment including cardiovascular disease, diabetes, and osteoporosis. The Committee considered that it was important to quantify the impact of these long-term effects.

Suitability

11.28. The Committee noted that there is a subcutaneous tocilizumab formulation commercially available in addition to the intravenous formulation. The Committee considered that utilising the subcutaneous infusion would eliminate the infusion costs considered above. The Committee also considered that funding the subcutaneous formulation would aid Pharmac's goal to provide equitable access to pharmaceutical care – noting that subcutaneous formulations are often considered more acceptable to recipients than intravenous infusions.

Cost and savings

11.29. The Committee considered that the financial impact of funding tocilizumab for PMR would depend on the target population for funding, as determined by the Special Authority criteria. The Committee noted that it was unclear from the available evidence how long individuals with PMR should be treated with tocilizumab, and considered further evidence is required to define the intended treatment duration.

11.30. The Committee considered that long-term benefits of funding tocilizumab for PMR may include a reduction in costs associated with the long-term impacts of glucocorticoids including diabetes, cardiovascular disease, and osteoporosis.

Funding criteria

11.31. The Committee considered that future funding criteria should be tailored to target the group who would receive greatest benefit from treatment with tocilizumab.

11.32. The Committee noted that it may be difficult to sufficiently define the intended population, and how this group could be defined to structure funding criteria, as many people experience negative effects from long term glucocorticoid treatment.

Summary for assessment

11.33. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for tocilizumab if it were to be funded in New Zealand for PMR. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

11.34. The Advisory Committee noted that elements of in the PICO (population, intervention, comparator, outcomes) for this application is unclear/uncertain at this

time. The PICO may develop based on new information, additional clinical advice, or further analysis by Pharmac staff

Population	People diagnosed with isolated PMR, who have trialled systemic glucocorticoids and methotrexate for at least three months, and have either a) experienced a disease flare despite treatment with methotrexate and tapering-dose prednisone, or b) have experienced intolerable side effects from these treatments
Intervention	Tocilizumab; the dosing and duration of treatment is unclear at this time. Glucocorticoid treatment to be administered in combination with tocilizumab, with a reduced dose of prednisone being a treatment goal.
Comparator(s) (NZ context)	Continued treatment with current treatment (prednisone +/- DMARDs) Treatment assumed to continue indefinitely.
Outcome(s)	The therapeutic intent of tocilizumab: - Symptom improvement for those who have experienced relapse on current treatment - Reduction in side effects from steroid treatment - Quality of life improvements, including in the SF-6D (per SEMAPHORE) - Reduction in prednisone dose, and an increase in the proportion of people who are steroid-free
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the target population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

12. Adalimumab, etanercept, and secukinumab for the treatment of psoriatic arthritis: removal of Special Authority criteria relating to CRP and ESR [P-001735]

Application

12.1. The Advisory Committee reviewed a Pharmac initiated proposal from Pharmac staff outlining proposed changes to the access criteria for biologic therapies for the treatment of psoriatic arthritis.

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

Recommendation

12.3. The Advisory Committee **recommended** that the current Special Authority criteria be changed with a **high** priority within the context of rheumatology treatments for treatment of psoriatic arthritis. The changes recommended to the current secukinumab Special Authority criteria for psoriatic arthritis are as follows (deletions in ~~strikethrough~~, additions in **bold**):

Initial application — (psoriatic arthritis) only from a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:
Either:
1 Both:
- 1.1 Patient has had an initial Special Authority approval for adalimumab, etanercept or infliximab for psoriatic arthritis; and
- 1.2 Either:
  - 1.2.1 Patient has experienced intolerable side effects from adalimumab, etanercept or infliximab; or
  - 1.2.2 Patient has received insufficient benefit from adalimumab, etanercept or infliximab to meet the renewal criteria for adalimumab, etanercept or infliximab for psoriatic arthritis; or

2 All of the following:
- 2.1 Patient has had severe active psoriatic arthritis for six months duration or longer; and
- 2.2 Patient has tried and not responded to at least three months of oral or parenteral methotrexate at a dose of at least 20 mg weekly or a maximum tolerated dose; and
- 2.3 Patient has tried and not responded to at least three months of sulfasalazine at a dose of at least 2 g per day or leflunomide at a dose of up to 20 mg daily (or maximum tolerated doses); and
- 2.4 Either:
  - 2.4.1 Patient has persistent symptoms of poorly controlled and active disease in at least 15 swollen, tender joints; or
  - 2.4.2 Patient has persistent symptoms of poorly controlled and active disease in at least four joints from the following: wrist, elbow, knee, ankle, and either shoulder or hip~~; and~~
- ~~2.5 Any of the following:~~
  - ~~2.5.1 Patient has a C-reactive protein level greater than 15 mg/L measured no more than one month prior to the date of this application; or~~
  - ~~2.5.2 Patient has an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour; or~~
  - ~~2.5.3 ESR and CRP not measured as patient is currently receiving prednisone therapy at a dose of greater than 5 mg per day and has done so for more than three months~~.

12.4. The Advisory Committee recommended that equivalent changes as recommended for secukinumab (above) be made to the adalimumab (Amgevita) and etanercept Special Authority criteria for psoriatic arthritis.

12.5. The Advisory Committee considered the following in making this recommendation:

- CRP is not an accurate marker of disease severity, and those with non-elevated CRP may have high disease activity that would be most appropriately treated with biologics
- Inclusion of CRP in the criteria is a barrier for people with non-elevated CRP with psoriatic arthritis as those with elevated and non-elevated CRP have similar health need
- ESR is rarely used for assessing inflammatory disease activity in people with psoriatic arthritis
- An estimated 80-90% of those unable to access biologic treatment due to non-elevated CRP or ESR are assumed to be using prednisone to access biologics.

12.6. The Advisory Committee noted that it had made separate recommendations during the meeting regarding biologic DMARDs in the treatment of psoriatic arthritis' Special Authorities' criteria relating to the number of prior conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) required, and that the above recommended changes to the Special Authority criteria needed to take those separate changes into account.

Discussion

Māori impact

12.7. The Committee discussed the impact of changing the Special Authority criteria of adalimumab, etanercept, and secukinumab for the treatment of psoriatic arthritis (PsA) on Māori health areas of focus and Māori health outcomes. The Committee considered that the removal of the C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and prednisone criteria would mean that Special Authority access would not require blood tests and so would reduce barriers in particular for those who experience additional systemic barriers when accessing medicines, such as Māori. The Committee considered that the impact of these changes on reducing inequities between Māori and non-Māori was not able to be estimated.

Background

12.8. The Committee noted that this funding proposal was initiated as a result of previous recommendations made by the then Rheumatology Subcommittee in May 2021, when reviewing the CRP criterion in the adalimumab and etanercept Special Authority criteria, for the initiation of these respective treatments in rheumatoid arthritis. The Committee noted that individuals with PsA often present with a normal CRP and so removal of this criteria would result in fewer courses of prednisone required prior to accessing biologic treatment.

12.9. The Committee noted that the current Special Authority criteria for adalimumab, etanercept, or secukinumab for PsA require a person to have an elevated CRP (>15 mg/L) or (ESR) (>25 mm/hour) or be taking at least 5 mg of prednisone.

Health need

12.10. The Committee considered that neither an elevated CRP nor ESR were good indicators of PsA disease activity. The Committee considered that having a high CRP confers a greater risk of subsequent joint damage but that low CRP does not correlate with low disease activity. The Committee considered that number and location of affected joints, skin involvement, and location were important indicators of disease activity (symptom burden and functional impact) in PsA. The Committee considered that there is evidence to support that higher CRP predicts structural damage and therefore people with high CRP have a worse disease prognosis.

12.11. The Committee considered that the use of prednisone to allow access to first line biologic disease modifying anti-rheumatic drugs (DMARDs) in those with non-elevated CRP or ESR in those with moderate to severe PsA poses an increased risk of erythrodermic psoriasis, which can be severe and often requires hospitalisation upon tapering of prednisone. The Committee considered that those with PsA often have associated comorbidities that contraindicate the use of prednisone or increase the risk of adverse effects from prednisone, including hyperglycaemia, weight gain, osteoporosis, cataracts, risk of infection, and risk of erythrodermic psoriasis flare, increasing the barriers for these people to access funded treatment. The Committee considered that those who are treated with prednisone to access biologic treatment (adalimumab, etanercept, or secukinumab) could experience a decrease in their disease activity that results in them no longer seeking access to more appropriate, long-term biologic treatment. The Committee considered that prednisone was not a long-term option for the treatment of PsA. The Committee noted that the use of glucocorticosteroids is included with caution recommended in the European League Against Rheumatism (EULAR) guidelines 2019 (Gossec et al. Ann Rheum Dis. 2020;79:700-12).

12.12. The Committee considered that the health need of those with elevated or non-elevated CRP or ESR is the same because the location and number of joints are a better indicators of disease activity in those with PsA and this requirement would not be changed in the Special Authority criteria. The Committee considered that compared with rheumatoid arthritis, CRP and ESR are less relevant in relation to PsA disease activity.

Health benefit

12.13. The Committee noted that pivotal trials for adalimumab (Mease et al. Arthritis Rheum. 2005;52:3279-89; Gladman et al. Arthritis Rheum. 2007;56:476-488), etanercept (Mease et al. Lancet. 2000;356:385-90; Mease et al. Arthritis Rheum. 2004; 50:2264-72) and secukinumab (Mease et al. N Engl J Med 2015;373:1329-39; Mease et al. Lancet. 2015;386:1137-46) were considered by PTAC in 2006 (adalimumab and etanercept) and 2018 (secukinumab). The Committee considered that these trials demonstrated benefit for these agents and considered that participants included in the pivotal trials considered inclusion criteria based on CRP or ESR. The Committee noted that the inclusion criteria of these trials did not require an elevated CRP or ESR to enter the trial. The Committee considered that the selection of patients with a higher baseline CRP or ESR could have been preferred due to a perception that they are more likely to respond to treatment. The Committee considered that those with non-elevated CRP or ESR were likely to benefit as reported in the pivotal trials.

12.14. The Committee considered that most published randomised controlled trials using these agents in PsA did not require elevated CRP or ESR in the inclusion criteria. The Committee considered that Houttekiet et al (Houttekiet et al. RMD Open. 2022;8(1):e001756) reported benefit in those with non-elevated CPR or ESR. The Committee considered that the benefit reported in the pivotal trials could be extrapolated to those with a non-elevated CRP or ESR.

12.15. The Committee considered that the results of the DISCOVER 2 trial (Mease et al. Lancet. 2020;395:1126-36) reporting the response to guselkumab in people with PsA stratified by low (<20 mg/L) or high (≥20 mg/L) baseline CRP were extrapolatable to those being treated with adalimumab, etanercept, or secukinumab for PsA as the clinical benefit is similar between the agents.

12.16. The Committee noted a study suggesting that there is greater response to TNF-inhibitor treatment in those people who have elevated CRP (Gratacós et al. Ann Rheum Dis. 2007;66:493-7). The Committee considered that the composite outcome (ACR50) to measure the impact of treatment included CRP within the composite and therefore biased the reported results. The Committee noted that it reported that the absence of arthritis in large joints also positively influenced the likelihood of experiencing a good therapeutic response. The Committee considered that this was unlikely to be accurate.

12.17. The Committee considered that there was reasonable evidence to suggest that elevated CRP was generally predictive of structural damage long-term, and that it was likely that those people with non-elevated CRP would therefore be likely be at slightly lower risk of long-term structural damage. The Committee considered that while there was some evidence that indicated there may be a superior response to treatment experienced by those people with higher CRP, this is uncertain given the instruments used to measure disease activity.

Cost and savings

12.18. The Committee considered there would be reduced costs from not requiring prednisone treatment to access adalimumab, etanercept, or secukinumab due to a reduction in the adverse effects relating to the use of prednisone.

12.19. The Committee considered that the number of people accessing adalimumab, etanercept, and secukinumab would not significantly increase as a result of the removal of CRP, ESR, and prednisone criteria for PsA. The Committee considered it reasonable to estimate that 80-90% of those unable to access biologic treatment due to non-elevated CRP or ESR would use prednisone to access funded treatment. The Committee considered that the similar changes to the rheumatoid arthritis criteria for adalimumab and etanercept did not significantly change the volume of adalimumab or etanercept dispensed.

Funding criteria

12.20. The Committee noted that these proposed criteria changes were in line with the rheumatoid arthritis changes made for adalimumab and etanercept. The Committee considered the approval periods for adalimumab, etanercept or secukinumab for rheumatology indications should be aligned to reduce the time burden of re-application on practitioners. The Committee considered that the continued prescribing of treatments was not determined by the length of the Special Authority approval period, and if a treatment was no longer effective then prescribers would consider other funded options.

12.21. The Committee considered the CRP criterion was not relevant to the level of disease activity in PsA and the use of prednisone to bypass this criterion was not in the person receiving treatment's best interest.

12.22. The Committee considered that the inclusion of the ESR criterion was impractical as it is rarely used for assessing inflammatory disease activity and laboratories do not approve the use of this test for PsA. The Committee therefore considered that removing the ESR criterion would not have any significant implications in clinical practice.

12.23. The Committee considered that the removal of the CRP, ESR, and prednisone criteria would mean that Special Authority access would not require blood tests and so would reduce barriers in particular for those who experience additional systemic barriers when accessing medicines, such as Māori or Pacific peoples.

Summary for assessment

12.24. The Advisory Committee considered that the below table summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for adalimumab (Amgevita), etanercept, and secukinumab if they were to be funded in New Zealand for psoriatic arthritis without the CRP, ESR or prednisone related criteria. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with severe psoriatic arthritis with CRP <15 mg/L or ESR <25 mm/hour who have received inadequate benefit from prior DMARDs
Intervention	First-line biologic treatments (adalimumab, etanercept, secukinumab)
Comparator(s) (NZ context)	Either: a) Low-dose prednisone for three months, followed by first-line biologics OR b) No biologic treatment 80-90% of these individuals are assumed to receive prednisone in order to access biologics
Outcome(s)	For those currently receiving prednisone and then biologics: - Earlier biologic treatment - Reduction in adverse events related to short-term (3 months) low-dose corticosteroids, and the quality of life/cost impacts of these adverse events - Biologic treatment assumed to be associated with reduction in symptoms vs low- dose corticosteroids For those currently receiving no biologic treatment - Benefits associated with biologic treatment vs no treatment, including improvement in symptoms and reduction in long-term joint damage - Risk of long-term structural damage assumed to be marginally lower for those with non-elevated CRP compared to those with high CRP

Table definitions:

Population: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)

Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).

Comparator: Details the therapy(s) that the target population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).

Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.

13. Adalimumab, etanercept and secukinumab - Psoriatic arthritis - review of SA criteria relating to number of csDMARDs previously trialled [P-001905]

Application

13.1. The Advisory Committee reviewed a paper from Pharmac staff regarding a number of requests for changes to the access criteria for biologic therapies for the treatment of psoriatic arthritis.

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

Recommendation

13.3. The Advisory Committee **recommended** with a **low priority** that the current Special Authority criteria in Section B (with equivalent changes in Section H) be

amended within the context of rheumatology treatments for treatment of psoriatic arthritis. The changes recommended to the current secukinumab Special Authority criteria for psoriatic arthritis are as follows (deletions in ~~strikethrough~~, additions in **bold**):

Initial application — (psoriatic arthritis) only from a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:
Either:
1 Both:
- 1.1 Patient has had an initial Special Authority approval for adalimumab, etanercept or infliximab for psoriatic arthritis; and
- 1.2 Either:
  - 1.2.1 Patient has experienced intolerable side effects from adalimumab, etanercept or infliximab; or
  - 1.2.2 Patient has received insufficient benefit from adalimumab, etanercept or infliximab to meet the renewal criteria for adalimumab, etanercept or infliximab for psoriatic arthritis; or

2 All of the following:
- 2.1 Patient has had severe active psoriatic arthritis for six months duration or longer; and
- **2.2 Patient has tried but experienced an inadequate response to at least three months of one of the following: methotrexate, sulfasalazine, or leflunomide, at a maximum tolerated dose; and**
- ~~2.2 Patient has tried and not responded to at least three months of oral or parenteral methotrexate at a dose of at least 20 mg weekly or a maximum tolerated dose; and~~
- ~~2.3 Patient has tried and not responded to at least three months of sulfasalazine at a dose of at least 2 g per day or leflunomide at a dose of up to 20 mg daily (or maximum tolerated doses); and~~
- 2.4 Either:
  - 2.4.1 Patient has persistent symptoms of poorly controlled and active disease in at least 15 swollen, tender joints; or
  - 2.4.2 Patient has persistent symptoms of poorly controlled and active disease in at least four joints from the following: wrist, elbow, knee, ankle, and either shoulder or hip; and
- 2.5 Any of the following:
  - 2.5.1 Patient has a C-reactive protein level greater than 15 mg/L measured no more than one month prior to the date of this application; or
  - 2.5.2 Patient has an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour; or
  - 2.5.3 ESR and CRP not measured as patient is currently receiving prednisone therapy at a dose of greater than 5 mg per day and has done so for more than three months.

13.4. The Advisory Committee **recommended** that equivalent amendments as recommended for secukinumab (above) be made to the adalimumab (Amgevita) and etanercept eligibility criteria for psoriatic arthritis.

13.5. In making this recommendation, the Advisory Committee considered the potential inequities between indications and differences in efficacy of conventional synthetic DMARD treatments.

13.6. The Advisory Committee noted that it had made separate recommendations during the meeting regarding for the eligibility criteria for biologic DMARDs in the treatment of psoriatic arthritis relating to C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) indices, and that the above recommended amendments to the eligibility criteria needed to take those separate changes into account.

Discussion

Māori impact

13.7. The Committee discussed the impact of amending the eligibility criteria of adalimumab, etanercept, and secukinumab for the treatment of psoriatic arthritis on Māori health areas of focus and Māori health outcomes. The Committee considered that a reduced number of eligibility criteria would reduce barriers in accessing biologics. The Committee considered that the impact of this on inequities between Māori and non-Māori was not able to be estimated.

Background

13.8. The Committee noted that currently a three-month trial of two conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) is required before accessing funded biologic treatment. The Committee noted that the current funded csDMARDs are methotrexate, leflunomide, and sulfasalazine.

13.9. The Committee noted that it has previously recommended a reduction in the number of trialled csDMARDs required before accessing funded biologic treatment for rheumatoid arthritis, and that this proposal is currently ranked on Pharmac's Options For Investment list.

Funding criteria

13.10. The Committee noted that the number of csDMARDs required to be trialled to access the same agents in rheumatoid arthritis is three and in ankylosing spondylitis is phrased simply as a trial of NSAIDs. The Committee noted that these differences were is based on the different evidence for efficacy for the respective indications.

13.11. The Committee noted that children only required a trial of one csDMARD for psoriatic arthritis prior to accessing funded biologic treatment. The Committee considered that there was an inequity in the access between adults and children.

13.12. The Committee considered that it was reasonable to have a trial of two csDMARDs before biologic treatment, as this gives the opportunity to consider the potential benefit of other csDMARDs before moving to biologic treatment. However, the Committee considered that it also follows that if a person being treated with csDMARD(s) experiences a partial treatment response, they might not then meet the criteria for biologic treatment. The Committee however considered that biologic treatment would be both clinically appropriate in people with a partial response to csDMARDs and would in addition reduce the potential for adverse effects from continuing csDMARDs.

13.13. The Committee considered there to be few appropriate csDMARD options for pregnant people, with leflunomide and methotrexate being contraindicated in pregnancy. The Committee considered that leflunomide, in particular, is an issue for those of childbearing potential as the recommended time after ceasing leflunomide before becoming pregnant is two years. The Committee considered that the use of leflunomide in those of childbearing potential as a second line csDMARD could affect the time for them to have children with potential flare with withdrawal and wash out.