PHARMAC
TE PĀTAKA WHAIORANGA

PHARMACEUTICAL SCHEDULE APPLICATION

To: PTAC

From: Funding Application Advisor

Date: May 2022

Upadacitinib – for the treatment of psoriatic arthritis (PsA) following inadequate benefit from at least one biologic [P-001741] and for the treatment of PsA following inadequate benefit from at least two biologics [P-001774]

SUMMARY OF PHARMACEUTICAL			
Brand Name	RINVOQ	**Chemical Name**	Upadacitinib
Indications	For the treatment of psoriatic arthritis (PsA) in adult patients which has responded inadequately to prior bDMARD use	**Presentation**	15 mg modified-release tablet
Therapeutic Group	Immunosuppressants	**Dosage**	15 mg once daily
Supplier	AbbVie Ltd	**Application Date**	November 2021
MOH Restrictions	Prescription medicine	**Proposal type**	Widen listing
Current Subsidy	Gross $1,271 per 28 15mg tablets (net $S 9(2)(b) per 28 tablets)	**Proposed Restriction**	Special Authority
Proposed Subsidy	Same as above	**Approved by Medsafe for this indication**	Yes
Market Data	Year 1	Year 2	Year 3
Number of Patients†	284	538	814
Net Cost to Schedule†	$S 9(2)	$S 9(2)	$S 9(2)
Net Cost to DHBs* (5-year NPV, 8%)	$S 9(2)		

DHBs, District health board; MOH, Ministry of Health; NPV, Net Present Value.
†Pharmac estimate
*Combining the cost to the Schedule and cost to DHBs.

QUESTIONS TO PTAC

Note to PTAC members: These questions have been identified by Pharmac staff as being particularly relevant to the application. Please feel free to provide additional information as appropriate.

Need

1. Considering the currently available treatments for psoriatic arthritis (PsA), is there an unmet health need? If so, why?
2. How severe is the health need of patients with PsA?
   2.1. What is the strength and quality of evidence for these needs?
3. Is PsA associated with higher mortality? Is the risk of mortality greater in patients with more active disease?
4. What's the Committee's view of the current treatment paradigm for PsA in New Zealand?
   4.1. Is the treatment sequence accurate?
   4.2. Pharmac estimates that 20-25% of patients initiating biologic treatment for PsA start on secukinumab, based on Special Authority data. Is this reasonable?
   4.3. Is the proportion of patients receiving secukinumab first-line likely to increase in the future? If so, by how much?
5. What are the health needs of families and whānau of people with PsA (including long-term effects) or of wider society? How severe are these needs?
   5.1. What is the strength and quality of evidence for these needs?
6. Does PsA disproportionally affect:
   - Māori?
   - Pacific people?
   - Other groups already experiencing health disparities relative to the wider New Zealand population (eg. NZ Dep 9-10 deprivation, refugees/asylum seekers)?

   6.1. What is the strength and quality of evidence?

Health benefit

7. Does upadacitinib as second-line treatment for PsA provide any additional health benefit or create any additional risks compared with other funded treatment options (noting the indirect treatment comparison with secukinumab)? If so, what benefits or risks are different from alternative treatments?
8. Is there evidence of a benefit from upadacitinib as third-line treatment for PsA?
   - Are the benefits/risks any different to those when it is used as a second-line treatment?
9. Would the fact that upadacitinib is a targeted synthetic make a difference to likely response rates compared with current funded biologics?
10. Which patient population would benefit most from upadacitinib for PsA?

11. What is the strength and quality of evidence, including its relevance to NZ, for health benefits that may be gained from upadacitinib for PsA ?

12. Would upadacitinib produce a health benefit for family, whānau or wider society, additional to the health benefits for people with PsA? If so how, and what is the strength and quality of evidence for this benefit?

13. If upadacitinib were to be funded for PsA, are there any consequences to the health system that have not been noted in the application or in this paper?

Suitability

14. Are there any non-clinical features of the upadacitinib (eg formulation, size, shape) that may impact on use, either by the patient, by family, or by healthcare workers, that have not been considered in the application?

Costs and savings

15. Does the information in the PICO table (**Table 5**) accurately reflect the intended population, intervention, comparator and outcome, if upadacitinib were to be funded for psoriatic arthritis? If not, how should this be adjusted?

    15.1. Is the treatment sequence for the intervention in the PICO appropriate?

    15.2. Would upadacitinib primarily be used after failure of one prior biologic, if listed second-line?

    15.3. How should the PICO table be amended if upadacitinib were listed third-line for PsA?

    15.4. Would patients who receive secukinumab first-line receive upadacitinib second-line (i.e. prior to an anti-TNF)?

16. Do some patients remain on treatment despite not demonstrating the 50% reduction in swollen joints required to meet the renewal criteria for biologics for psoriatic arthritis?

    16.1. Would it be reasonable to assume that patients who receive smaller benefits from treatment (e.g. a 20% improvement) would remain on their treatment?

17. Regarding upadacitinib for PsA, is it reasonable to assume that:

    17.1. Response is associated with a reduction in health resource utilisation (e.g. outpatient visits, inpatient admissions, ED visits)?

    17.2. Patients who gain a response to biologics or upadacitinib require fewer hospitalisations / outpatient visits / ED visits?

    17.3. Do the answers to any of the above regarding upadacitinib differ from current funded biologics?

18. Is there likely to be a prevalent group of patients who switch to upadacitinib upon listing?

    18.1. If so, is this group likely to be similar in size to the prevalent group who initiated secukinumab?

    18.2. Is the speed of uptake of upadacitinib likely to be similar to that of secukinumab?

19. Among patients with inadequate response to a first-line bDMARD, is upadacitinib (or secukinumab) associated with greater efficacy than a second anti-TNF?

20. Would the use of upadacitinib create any significant changes in health-sector expenditure other than for direct treatment costs (e.g. diagnostic testing, nursing costs or treatment of side-effects)?

General

21. Is there any data or information missing from the application, in particular clinical trial data and commentary?

22. Is further evidence or information required to assess the benefits/risks of upadacitinib in the third-line for AS? If so, what is needed?

Recommendations

23. Should upadacitinib be listed in the Pharmaceutical Schedule for the **second-line** treatment of PsA?

    - Name the Factors for Consideration particularly relevant to a positive or negative recommendation and explain why each is relevant.
    - If listing is recommended, what priority rating would you give to this proposal? **[low / medium / high / only if cost-neutral]**?
    - Are the proposed Special Authority criteria appropriate? If not, how should these be amended?

24. Should upadacitinib be listed in the Pharmaceutical Schedule for the **third-line** treatment of PsA?

    - Name the Factors for Consideration particularly relevant to a positive or negative recommendation and explain why each is relevant.
    - If listing is recommended, what priority rating would you give to this proposal? **[low / medium / high / only if cost-neutral]**?
    - Are the proposed Special Authority criteria appropriate (eg regarding duration of initial approval and maximum dosing)? If not, how should these be amended?

25. Should Pharmac seek any further advice to inform its assessment of this application? If so, what advice and from whom?

26. Does the Committee have any recommendations additional to the application?

PURPOSE OF THIS PAPER

The purpose of this paper is to seek advice from the Committee regarding an application from AbbVie Ltd for the use of upadacitinib (Rinvoq) for the **second-line** treatment for adult patients with psoriatic arthritis (PsA) who have received inadequate benefit from at least one prior biologic disease modifying antirheumatic drug (bDMARDs).

Pharmac staff are also interested in the Committee's view of the potential benefits and risks of upadacitinib for the **third-line** treatment for adult patients with PsA who have received inadequate benefit from prior disease modifying antirheumatic drugs including two bDMARDs.

Note: Upadacitinib is not a biologic treatment (rather a targeted synthetic) but for readability in this paper, we refer to biologic treatments and have include targeted synthetics within this.

DISCUSSION

BACKGROUND

Previous consideration of treatments for psoriatic arthritis (PsA)

Table 1: Summary of consideration of treatments for PsA.

Pharmaceutical	Mechanism of action	Treatment line/detail	Status
Adalimumab	Tumour necrosis factor (TNF) inhibitor	First biologic line	Funded in 2009. Access criteria amended in 2011. Current criteria here.
Etanercept	TNF inhibitor	First biologic line (allowing eligible patients to access adalimumab and etanercept in any order)	Funded in 2010. Current criteria here.
Golimumab	TNF inhibitor	Second-line	PTAC recommended declining the application. Inactive application was declined by Pharmac in 2020.
Infliximab	TNF inhibitor	Second or third line	Funded; current criteria here.
Secukinumab	Inhibitor of proinflammatory cytokine interleukin-17A (IL-17A)	First and second biologic line	Funded for first-line or second-line in 2021. Current criteria here.

Previous consideration of upadactinib

Upadacitinib has previously been considered by PTAC as follows:

- Moderate to severe rheumatoid arthritis (recommended with Medium priority by PTAC in February 2021)

- Moderate to severe atopic dermatitis (recommended with High priority by PTAC in November 2021)

Upadacitinib was listed in Section B and Section H in 2021 in response to the imminent tocilizumab stock shortage as a later-line treatment for rheumatoid arthritis, subject to funding criteria. Funding of a wider group of people with rheumatoid arthritis remains under assessment.

Another new application for upadacitinib for ankylosing spondylitis in adult patients who have received inadequate benefit from prior biologic disease modifying antirheumatic drug (bDMARD) use is on the concurrent PTAC agenda.

Need

Description of the disease

Psoriasis is a common skin disease occurring in 3% of adults and <1% of children. Psoriatic arthritis (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). Often about a decade (and sometimes longer) passes between diagnosis of the skin disease and subsequent joint disease diagnosis. Manifestations of PsA most commonly include the peripheral joints, axial skeleton, skin and entheses (eg dactylitis). The gut and lung may also be affected. 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.

PsA most frequently presents as polyarthritis, involving peripheral and/or axial joints. The clinical manifestations of the disease can change over time as the disease progresses. Radiographic evidence of joint erosion develops over time and the number of involved joints can increase. While it is a heterogenous disease, PsA can become more destructive and disabling over time. Risk factors for progressive damage and poor prognosis in PsA include an increased number of actively inflamed joints, markers of inflammation (eg C-reactive protein, CRP), clinical or radiologic evidence of joint damage, failure of medication trials, and diminished quality of life.

Initial treatment with conventional synthetic (non-biologic) DMARDs will be inadequate for up to a quarter of patients, and most of these will require funded treatment with a biologic DMARD (bDMARD). PTAC has previously estimated that estimated that only 70% of patients who try biologics will have an adequate clinical response, and some patients are resistant to all three funded TNF-α inhibitors (PTAC, February 2018).

Epidemiology

PsA affects males and females equally. The supplier has stated that the prevalence of psoriasis is 3% in the adult population; of these, the supplier estimates 15-25% have PsA and about a quarter of those receive an insufficient benefit from conventional synthetic DMARDs. As of September 2021, there were 860 patients with PsA in New Zealand who

were prescribed a bDMARD for PsA, with annual growth of 9%. Based on 30% of patients with PsA receiving an inadequate response from bDMARDs, approximately 307 patients would be eligible for second-line biologic treatment.

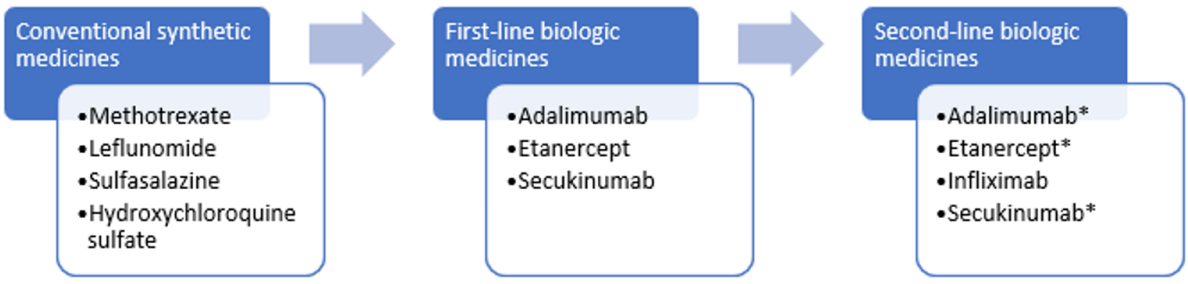
The health need of the person

PsA is a heterogenous disease and symptoms can depend on the disease activity and severity. Progressive damage caused to axial and peripheral joints leads to physical deformability and disability. Pain is one of the most commonly reported symptoms in patients with PsA and is associated with a decrease in quality of life in PsA, as previously noted by PTAC in 2018. Fatigue is another common symptom of the disease. Individuals may have both psoriasis and PsA and therefore have a greater disease burden. It is reported that patients with PsA have higher rates of depression and anxiety compared with rates in patients with psoriasis, rheumatoid arthritis or ankylosing spondylitis.

There is an increased risk of cardiovascular disease in patients with PsA (Ogdie et al. Ann Rheum Dis. 2015;74:326-32). According to UpToDate, psoriasis is associated with a number of comorbidities including an increased risk of the metabolic syndrome, hypertension, diabetes, atherosclerosis, malignancy, hepatic and pulmonary disorders, and psychiatric disease (particularly prevalent are anxiety and depression). Metabolic syndrome is reported to be related to PsA severity and occurs frequently in PsA (Haroon et al. J Rheumatol. 2014;41:1357-65; Haroon et al. J Rheumatol. 2016;43:463-4). Liver abnormalities including fatty liver disease are also reported to be more common in patients with PsA than those without it and this appears to be associated with more severe disease (Pakchotanon et al. J Rheumatol. 2020;47:847-53).

The availability and suitability of existing medicines, medical devices and treatments

There are currently a number of funded conventional synthetics and biologics available to treat PsA. Patients with a confirmed diagnosis of PsA will have tried two or more conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) before using adalimumab and/or etanercept. The supplier considers that the majority of patients with PsA will commence on adalimumab or etanercept in the first line, with secukinumab used in the second line setting. The current options in the treatment paradigm for patients with PsA, according to the supplier, is as follows (shown below in **Figure 1**):



Source: Adapted from PHARMAC 2021a
Note: *if not trialled in first line

Figure 2: Illustration of current clinical management of PsA in New Zealand as permitted by Pharmac Special Authority criteria Proposed treatment paradigm (Source: Supplier application).

Pharmac staff consider the current treatment sequence for such patients could be:

1. *First line anti-TNF (typically adalimumab) --> 2. Secukinumab --> 3. Second anti-TNF --> supportive care.*

A summary of the supplier's view of the location of each agent in the treatment paradigm, Pharmac staff's view of the same, and current market usage data is below in **Table 2**. We seek the Committee's view of the paradigm, treatment sequence, and whether it is reasonable to assume that after failure of first-line anti-TNF, patients switch to secukinumab instead of trialling another TNF inhibitor (etanercept or infliximab).

Table 2: Potential place in treatment sequence and current market share of treatments for AS.

Treatment	Supplier view of location in AS paradigm	Pharmac staff view of location in AS paradigm	Patients on treatment – 31 March 2022	Market share – 31 March 2022
Adalimumab	1. First-line option	1. First-line	740	51%
Etanercept	1. First-line option	3. Third-line	408	28%
Secukinumab	2. Second-line	2. Second-line	213	15%
Infliximab	3. Third-line	Unclear	78	5%

The health need of family, whānau, and wider society

As with any disorder with significant morbidity, there can be impacts on the health on family and whānau who care for the person. Pharmac acknowledges that there may be a health need for other people as a result for caring for patients with PsA, particularly as the disease progresses and pain and mobility worsen.

The impact on the Māori health areas of focus and Māori health outcomes

Analysis of the ethnicity of patients receiving biologic treatment for psoriatic arthritis over the past two financial years suggests that 7.6% of patients receiving biologics for psoriatic arthritis were Māori.

The impact on the health outcomes of population groups experiencing health disparities

Analysis of the ethnicity of patients receiving biologic treatment for psoriatic arthritis over the past two financial years suggests that 2.2% of patients receiving biologics for psoriatic arthritis were Pacific peoples. Pharmac is not aware of any other population groups experiencing health disparities who are disproportionately affected by PsA.

The impact on Government health priorities

The treatment of PsA, which is a long-term condition, aligns with the current Government health priorities.

Health Benefit

Details of the pharmaceutical under consideration

Clinical Pharmacology and Mechanism of Action

The four Janus Kinases (JAKs) - JAK1, JAK2, JAK3 and TYK2 - are important intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes including inflammatory responses, haematopoiesis and immune surveillance. Upadacitinib is an oral, selective, and reversible inhibitor of Janus Kinase-1 (JAK1), which is more potently inhibited by upadacitinib compared to JAK2 and JAK3. JAK1 is important in inflammatory cytokine signals while JAK2 is important for red blood cell maturation and JAK3 signals play a role in immune surveillance and lymphocyte function (Source: Rinvoq Data Sheet).

New Zealand Regulatory Approval

Upadacitinib is Medsafe-approved for the treatment of active PsA in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs (may be used as monotherapy or in combination with a non-biological DMARD).

It is also Medsafe approved for the following indications:

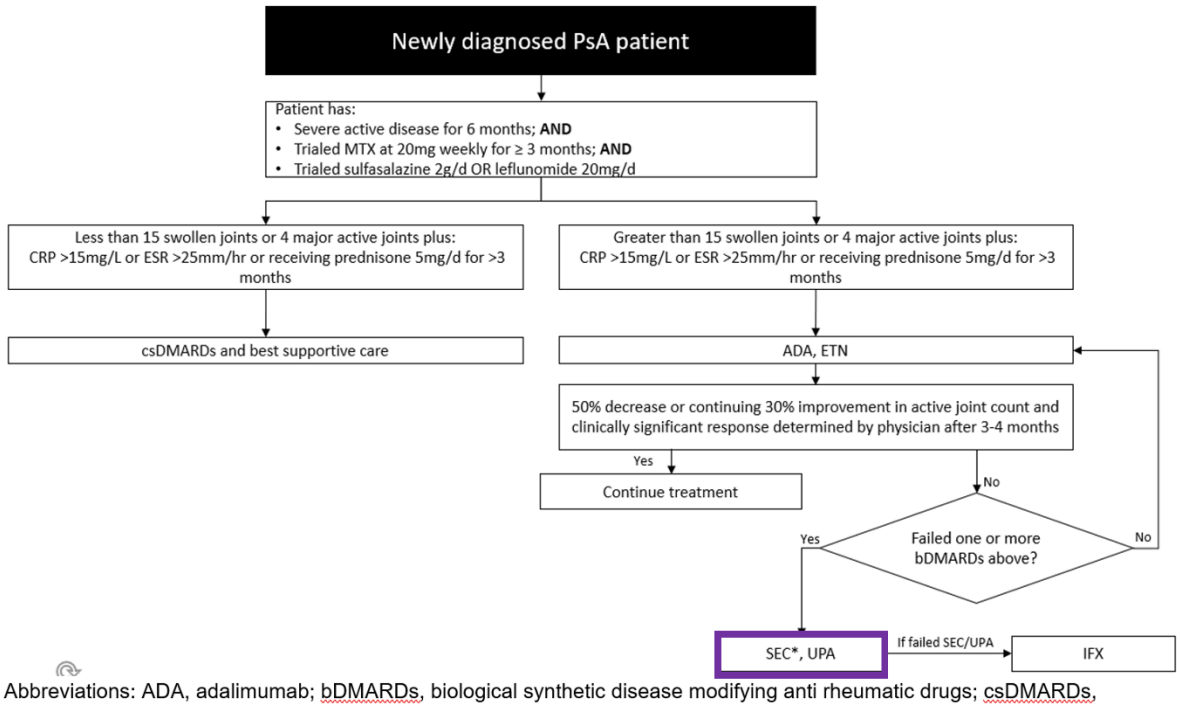
- the treatment of adults with moderately to severely active rheumatoid arthritis (may be used as monotherapy or in combination with methotrexate or other csDMARDs)
- the treatment of adults and adolescents 12 years and older with moderate to severe atopic dermatitis who are candidates for systemic therapy
- the treatment of active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy.

Recommended Dosage

Once-daily oral dose of 15 mg, taken with or without food. The supplier proposes ongoing treatment for PsA, with no maximum treatment duration. The 30 mg once daily dose was included in upadacitinib clinical trials but according to the supplier this dose is not being commercialised in PsA.

Proposed Treatment Paradigm

The supplier proposes upadacitinib be listed for second-line treatment of PsA, after treatment with a TNFi (ie adalimumab or etanercept). This would therefore be an alternative option to secukinumab in the second line with a different mechanism of action and mode of administration. The proposed treatment paradigm is presented in **Figure 2**, with upadacitinib (UPA) shown in the bold purple box. Pharmac staff seek the Committee's view of whether this reflects where upadacitinib would be expected to be accessed in the treatment paradigm, if it were to be funded for PsA (ie would patients prefer to try it earlier than depicted, ahead of other treatments in the paradigm?).



Abbreviations: ADA, adalimumab; bDMARDs, biological synthetic disease modifying anti rheumatic drugs; csDMARDs, conventional synthetic disease modifying anti rheumatic drugs; CRP, C-reactive protein test; ESR, Erythrocyte sedimentation rate; ETN, etanercept; IFX, infliximab; MTX, methotrexate; PsA, psoriatic arthritis; SEC, secukinumab; UPA, upadacitinib
* Secukinumab can also be used first line but this is expected to occur only in a small number of patients with skin involvement.

Figure 2: Proposed treatment paradigm (Source: Supplier application).

Proposed Special Authority Criteria

Second-line treatment

The supplier has proposed the following Special Authority criteria for upadacitinib for the **second-line treatment of PsA**, which Pharmac staff have made minor additions to for consistency with current criteria, as shown in **bold**. Pharmac staff consider that the proposed criteria would allow for upadacitinib to be accessed in several treatment lines. The final criterion specifying a maximum dose may be intended to manage the risk of anti-drug antibodies with biologics and mitigate the risk of increased dosing, which also may or may not be relevant for upadacitinib. We seek the Committee's advice on whether the proposed criteria would be appropriate for upadacitinib including these particular points.

> **Initial application — (psoriatic arthritis – 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:
> 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 **a reasonable trial of** adalimumab **and/**or etanercept; 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) 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 and 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 QD.

Third-line treatment

Pharmac staff have drafted the following Special Authority criteria for **third-line treatment of PsA,** based on the above criteria for second-line:

Initial application — (psoriatic arthritis – third-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:
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
    2.1. The patient has experienced intolerable side effects from **a reasonable trial of** two prior biologic therapies; or
    2.2. The patient has received insufficient benefit to meet the renewal criteria for the prior biologic therapies for psoriatic arthritis.

Renewal — (psoriatic arthritis – third-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. 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 and 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 QD.

International Recommendations

Table 3: International recommendations regarding the funding of upadacitinib for PsA

Country (HTA Agency)	Date	Outcome	Reason
Australia (PBAC)	March 2021	✓ The PBAC recommended upadacitinib for "the treatment of severe active PsA in patients who have failed to achieve an adequate response to conventional DMARDs".	Cost-effectiveness of upadacitinib would be acceptable if it were cost minimised to the lowest cost bDMARD for this indication. Nominated comparator of tofacitinib was reasonable, however all other bDMARDs currently listed for PsA were also relevant alternative therapies. Indirect comparison support a conclusion that upadacitinib is of non-inferior comparative effectiveness to tofacitinib (both ACR20 and ACR50 response)
Canada (CADTH - CDEC)	August 2021	✓ The CADTH recommended upadacitinib for "the treatment of adults with active PsA who have had an inadequate response or intolerance to methotrexate or other DMARDs". ✓ Upadacitinib may be used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs.	Evidence that upadacitinib is more effective than placebo at improving PsA symptoms May meet some of the needs that are important to patients (reduced joint pain, clearing psoriasis, improving HRQOL). Evidence to suggest upadacitinib is more effective than other reimbursed therapies. Budget impact ranged from $2.5m in savings to $3.1m cost.
Scotland (SMC)	No evidence of consideration by the SMC for PsA at the time this paper was written.		
England/Wales (NICE)	February 2022	✓ The NICE recommended upadacitinib for patients with PsA who have had 2 conventional DMARDs and at least 1 biological DMARD, or for whom TNFi are contraindicated ✓ Upadacitinib may be used as monotherapy or in combination with methotrexate	Evidence that upadacitinib is more effective than placebo for treating PsA and may be similarly as effective as adalimumab Results of an indirect comparison are uncertain but suggest that upadacitinib is likely to work as well as other bDMARDs Upadacitinib was not cost effective vs some bDMARDs for people who had not had a biological DMARD before Upadacitinib was cost effective for people who had had at least 1 biological DMARD or who could not have TNF-alpha inhibitors

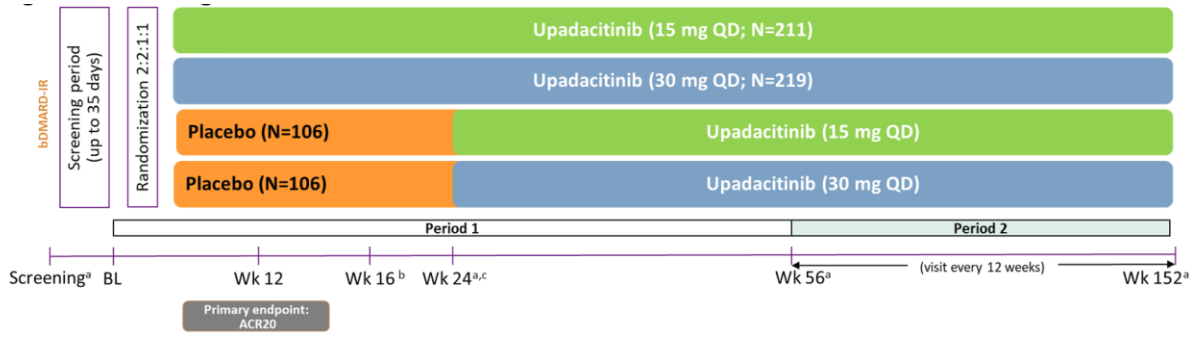
The health benefits to the person, family, whānau and wider society

Evidence Summary

The supplier has provided indirect evidence claiming non-inferior efficacy and comparable safety of upadacitinib versus its nominated comparator, secukinumab, for the second biologic line of treatment of PsA. A summary of the evidence is provided in the following table (**Table 4**). The full text publications are available in **Appendix 1.** This evidence comes from the following placebo-controlled trials:

Upadacitinib – SELECT-PsA 2

The main evidence for upadacitinib comes from the randomised, placebo-controlled SELECT-PsA 2 study. The design of this study is shown below in **Figure 3**.



Abbreviations: bDMARD, biologic disease modifying antirheumatic drugs; QD, once daily; UPA, upadacitinib.
Note: Patients were also on a stable background dose of csDMARD and inadequate responders to ≥1 bDMARD
[a.] All patients will receive x-rays of hands and feet at screening, Wk 24, Wk 56, Wk 104, and Wk 152/PD.
[b.] At Week 16, rescue therapy will be offered to patients classified as non-responders (defined as not achieving at least 20% improvement in either or both tender joint count (TJC) and swollen joint count (SJC) at both Week 12 and Week 16).
[c.] At Week 24, all placebo patients will switch to upadacitinib 15 mg QD or 30 mg QD (1:1 ratio) regardless of response.

Figure 3: Design of SELECT-PsA 2

Secukinumab - FUTURE 2, 3 and 5

The supplier has submitted evidence for secukinumab from the FUTURE 2, 3 and 5 studies. PTAC previously considered evidence from FUTURE-1 and FUTURE-2, and from six other studies using data from secukinumab trials to compare against other biologic treatments, in February 2018. At that time, PTAC noted:

- Studies sponsored by the supplier of secukinumab reported that secukinumab was superior, while the study sponsored by the supplier of adalimumab reported that adalimumab was superior. One independent study concluded that secukinumab was superior in some ways
- Infections were more common in secukinumab treatment groups in the FUTURE-1 trial but not in the FUTURE-2 trial, although a US report (Ibler et al. 2017) stated no difference in infection rates when compared with other biologics being used to treat plaque psoriasis
- The placebo-controlled studies were of high quality and strength in demonstrating clear evidence of benefit against placebo
- However, the comparison studies were indirect and contradictory, making assessment of relative efficacy difficult
- There is poor quality evidence of secukinumab's benefit compared to currently available biologic agents

- There was sufficient evidence of secukinumab's relative efficacy in PsA to recommend it at first biologic line with the same restrictions as currently apply to the TNF-inhibitors
- Also recommended that, due to the different mode of action to TNF-inhibitors, secukinumab be funded at 2nd biologic line following failure of a TNF-inhibitor
- An upcoming trial was being organised (the EXCEED trial) to compare secukinumab with adalimumab in patients with PsA was scheduled to be completed in March 2020.

Indirect treatment comparison

The supplier application incorporates an indirect treatment comparison of upadacitinib 15 mg vs secukinumab 300 mg. This concludes that, at weeks 12 and 24, upadacitinib 15 mg was non-inferior to secukimumab 300 mg in terms of ACR20/50/70 response, although point estimates favoured upadacitinib.

Table 4: Summary of key evidence for upadacitinib and evidence for secukinumab for the second-line treatment of PsA.

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety	Citation
Upadacitinib								
SELECT PsA 2	Randomised (2:2:1:1), placebo-controlled, double-blind, phase 3 trial	Adult patients with active PsA, ≥3 each of swollen and tender joints, and prior inadequate response from or intolerance to ≥1 bDMARD No. of previous bDMARDs ranged from 0-≥3. 1 previous bDMARD in 63.7% placebo, 59.7% upadacitinib 15 mg and 59.6% upadacitinib 30 mg	N = 642	Upadacitinib 15 mg OR upadacitinib 30 mg OR placebo followed by upadacitinib 15 mg at week 24 OR placebo followed by upadacitinib 30 mg at week 24 Stable background NSAIDs, corticosteroids, ≤2 non-bDMARDs permitted	24 weeks	Monotherapy in 52.8% placebo, 53.6% upadacitinib 15 mg and 55.0% upadacitinib 30 mg. **Primary endpoint -** proportion of patients achieving American College of Rheumatology (ACR) 20 response at week 12: 56.9% upadacitinib 15 mg, 63.8% upadacitinib 30 mg and 24.1% placebo; *P*<0.001 for both upadacitinib arms vs placebo. Response rates for upadacitinib 15 mg and upadacitinib 30 mg were 44.9% and 64.8% in the subgroup of patients who had failed >1 biologic DMARD and 55.8% and 66.7% in the subgroup of patients that were on monotherapy. Improvements in ACR50 and ACR70 observed with both upadacitinib doses versus placebo at week 12. The 15 mg and 30 mg doses of upadacitinib showed greater improvement versus placebo with respect to all key secondary endpoints. Change from baseline to week 12 in Health Assessment Questionnaire-Disability Index (HAQ-DI) – least squares mean difference -0.21 upadacitinib 15 mg and -0.31 upadacitinib 30 mg (*P*<0.001 for both vs placebo).	Most commonly reported treatment-emergent adverse events (TEAEs) were upper respiratory tract infection and nasopharyngitis in upadacitinib- treated patients. Serious AEs (SAEs) were reported in 4 (1.9%) placebo, 12 (5.7%) upadacitinib 15 mg and 18 (8.3%) upadacitinib 30 mg. Upadacitinib 15 mg: non-fatal myocardial infarction, pulmonary embolism (1 patient each)	Mease et al. Ann Rheum Dis. 2020;80:312-20
SELECT PsA 2 – 52 weeks	As above At week 16, background medications initiated/adjusted in patients who did not achieve ≥20% improvement in tender and swollen joint counts vs baseline.				56 weeks	479 (74.7%) upadacitinib and 560 (87.2%) placebo completed 56 weeks. ACR20/50/70 for upadacitinib 15 mg at week 56: 59.7%, 40.8% and 24.2% respectively. In both placebo to upadacitinib groups, responses at week 56 approached or were similar to those for patients who received upadacitinib from baseline.	Most common AEs same as previous. One upadacitinib 30 mg patient death. Malignancies in 10 upadacitinib 15 mg, 8 upadacitinib 30 mg.	Mease et al. Rheumatol Ther. 2021;8:903-19

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety	Citation
Secukinumab								
FUTURE 2	Randomised (1:1:1:1), double-blind, placebo-controlled phase 3 trial	Adult patients with active PsA, ≥3 each of swollen and tender joints, despite previous treatment with NSAIDs, DMARDs or TNFi No. of previous TNFi ranged from 0-3. Nil previous TNFi in about two-thirds. 1 previous bDMARD in 16% placebo, 16%, 26% and 21% secukinumab 300 mg, 150 mg and 75 mg, respectively.	N = 397	Subcutaneous (SC) secukinumab 300 mg OR secukinumab SC 150 mg OR secukinumab SC 75 mg OR placebo once a week to week 4 then 4-weekly. Placebo patients received (1:1) SC secukinumab 300 mg or 150 mg 4-weekly from week 16 or week 24 depending on response.	24 weeks	Concomitant oral corticosteroids and methotrexate were permitted. At week 16, patients were classified as responders (≥20% improvement from baseline in tender and swollen joint counts) or non-responders. 373 (94%) completed week 24 treatment. **Primary endpoint -** ACR20 response at week 24: 54% secukinumab 300 mg (p<0·0001), 51% secukinumab 150 mg (p<0·0001), and 29% secukinumab 75 mg (p=0·0399) vs placebo (15%) Change from baseline to week 12 in Health Assessment Questionnaire-Disability Index (HAQ-DI) – least squares mean difference: -0.31 placebo vs -0.25 secukinumab 300 mg (P=0.0040), -0.17 secukinumab 150 mg (*P*=0.0555), -0.01 secukinumab 75 mg (P=0.0.9195).	Similar incidence of AEs during the placebo-controlled period, except for a slightly higher incidence of SAEs with secukinumab 300 mg and 75 mg than secukinumab 150 mg or placebo. Most common infections: upper respiratory tract infections, nasopharyngitis. Candida infections in 11 secukinumab patients. No deaths reported. Squamous cell carcinoma (3), ulcerative colitis (2) and myocardial infarction (1) in secukinumab patients.	McInnes et al. Lancet. 2015;386:1137 46
FUTURE 2 – 2 years					104 weeks	86% 300 mg, 76% 150 mg and 66% 75 mg completed 104 weeks of treatment. ACR20 response at week 104 (after multiple imputation): 69.4% secukinumab 300 mg, 64.4% secukinumab 150 mg, and 50.3% secukinumab 75 mg. Responses were sustained regardless of prior TNFi use. Improvement in HAQ-DI scores sustained through week 104.	Consistent with previous. No deaths reported.	McInnes et al. Rheumatology (Oxford). 2017;56):1993-2003

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety	Citation
FUTURE 2 – 5 years	As described on previous page.				5 years	248/397 (62%) completed 5 years of treatment. ACR20 response at 5 years: 74% secukinumab 300 mg, 79% secukinumab 150 mg. Improvements in ACR20 and ACR50 responses were sustained in both patients naive to TNF inhibitors and those who were intolerant or received inadequate responses from TNF inhibitors, with generally higher responses observed in patients naive to these agents than in those with intolerance or inadequate response. Improvement in HAQ-DI sustained through to 5 years.	Serious infection was the most frequent treatment-emergent SAE with secukinumab. Two cases of major adverse cardiovascular events and one death (sepsis secondary to acute pancreatitis, secukinumab 150 mg).	McInnes et al. Lancet. 2020;2:E227-35
FUTURE 3	Randomised (1:1:1), double-blind, placebo-controlled phase 3 trial	Adult patients with active PsA, ≥3 each of swollen and tender joints, despite previous treatment with NSAIDs, DMARDs or TNFi No. of previous TNFi ranged from 0-3. Nil previous TNFi in about two-thirds.	N = 414	SC secukinumab 300 mg OR secukinumab SC 150 mg OR placebo once a week to week 4 then 4-weekly. Placebo patients received secukinumab 300 mg or 150 mg 4-weekly from week 16/24	52 weeks	Concomitant oral corticosteroids and methotrexate were permitted. **Primary endpoint -** ACR20 response at week 24: 48.2% secukinumab 300 mg (p<0·0001), 42.0% secukinumab 150 mg (p<0·0001) vs placebo (16.1%) ACR50 response rates at week 24 were higher with secukinumab 300 mg (34.5%; p<0.0001) and 150 mg (18.8%; p < 0.05) vs placebo (8.8%). ACR20/50 response rates higher with secukinumab vs placebo in TNFi-naïve and TNFi- intolerant/inadequate response patients (generally higher in TNFi-naïve). ACR20/50 responses sustained at week 52 (58.3%/33.1% in secukinumab 300 mg group and 47.1%/27.5% in secukinumab 150 mg group). Change from baseline to week 24 and 52, respectively, in HAQ-DI: least squares mean difference: -0.17 placebo (week 24 only) vs -0.38 and -0.43 secukinumab 300 mg and -0.27 and -0.30 secukinumab 150 mg.	Similar rates of treatment-emergent AEs across groups. Most common SAEs with secukinumab: infections and infestations (1.8%); musculoskeletal and connective tissue disorders (2.1%); neoplasms (1.6%). Two deaths reported with secukinumab 150 mg (pancreatic carcinoma, small cell lung cancer). Myocardial infarction in 1 patient. Malignant or unspecified tumours in 6 secukinumab patients. Inflammatory bowel disease (IBD) in 1.	Nash et al. Arthritis Res Ther. 2018;20:47

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety	Citation
FUTURE 5	Randomised (2:2:3:3), double-blind, placebo-controlled, phase 3 trial	Adult patients with active PsA, ≥3 each of swollen and tender joints, despite previous treatment with NSAIDs Included patients with prior TNFi use who received inadequate response or stopped TNFi due to safety or intolerance 70.4% of patients were TNFi-naïve	N = 996	Secukinumab 300 mg with loading dose (LD) OR secukinumab 150 mg with LD OR secukinumab 150 mg without LD OR placebo once a week to week 4 then 4-weekly. Placebo patients received secukinumab 300 mg or 150 mg 4-weekly from week 16/24	24 weeks	Concomitant oral corticosteroids and methotrexate were permitted. 66 (6.9%) had discontinued at week 24 (placebo n=37). **Primary endpoint -** ACR20 response at week 16: secukinumab 300 mg with LD (62.6%), 150 mg with LD (55.5%) or 150 mg without LD (59.5%) than placebo (27.4%; p<0.0001 for all doses vs placebo). ACR50/70 response rates at week 16 significantly higher with all secukinumab doses vs placebo. Change from baseline to week 16 in HAQ-DI: least squares mean difference: -0.21 placebo vs -0.55 secukinumab 300 mg with LD, -0.44 secukinumab 150 mg with LD and -0.45 secukinumab 150 mg without LD.	Most commonly reported AEs: upper respiratory tract infections. No deaths or major adverse cardiac events (MACE) were reported. Non-fatal SAE rates were low overall and similar for secukinumab (3.0%) and placebo (3.6%).	Mease et al. Ann Rheum Dis. 2018;77:890-897
FUTURE 5 – 52 weeks					52 weeks	86.6% of patients completed 52 weeks of treatment. ACR20 response at week 52 was 68.9, 64.1 and 65.8% in secukinumab 300, 150 and 150 mg no load groups, respectively. In the overall population, the radiographic progression rate was low at week 52 across all treatment groups.	Consistent with previous. No new or unexpected safety signals, no tuberculosis infections and no deaths were reported.	van der Heijde et al. Rheumatology (Oxford). 2020;59:1325-34
FUTURE 5 – 2 years					2 years	783 (78.6%) completed 2 years of treatment. Clinical improvements at week 16 sustained through 2 years in patients originally randomised to secukinumab who continued to receive secukinumab. Increases in ACR20 (56.5% to 72.7%) and ACR50 (33.9% to 48.1%) responses week 60 to week 104 in patients with dose escalation (150 mg no LD to 300 mg)	Consistent with previous. 3 MACE events were reported. IBD reported in 5 patients. 3 deaths reported (1 sepsis, 2 acute myocardial infarction and cardiorespiratory arrest).	Mease et al. RMD Open. 2021;7:e001600

Upadacitinib for first-line (1L), third-line (3L) treatment, and treatment sequencing

The submission also includes 1L evidence for upadacitinib from the Select-PsA 1 trial of upadacitinib vs adalimumab vs placebo in patients with active PsA who have a history of inadequate response to at least one conventional synthetic DMARD. Given that is not the indication under consideration, this evidence is not detailed in this paper.

Pharmac staff note the that EXCEED trial is now published. It is a randomised (1:1), double-blind, active-controlled, phase-3b, multicentre, 52-week study that investigated secukinumab monotherapy and adalimumab monotherapy in 853 patients with active PsA who were naive to biological therapy for PsA and psoriasis, and who were intolerant or received an inadequate benefit from csDMARDs. Secukinumab did not meet statistical significance for superiority vs adalimumab in terms of the primary outcome, ACR20 response at week 52 (67% secukinumab vs 62% adalimumab (odds ratio 1·30, 95% CI 0·98–1·72; *P*=0·0719) (McInnes et al. Lancet. 2020;395:1496-1505; **Appendix 2**).

For 3L treatment of PsA, Pharmac staff have performed a literature search for evidence in the 3L setting which is described subsequently and note that roughly one-third of patients in the SELECT-PsA 2 trial had received treatment with two previous bDMARDs.

In terms of treatment sequencing, UpToDate authors suggest that patients with PsA who switch to a second TNF inhibitor after resistance to the first TNFi may benefit after about three to four months of treatment. The authors also prefer to switch patients from an antibody-based agent (eg adalimumab, infliximab) to etanercept and vice versa, although there is limited evidence to inform this strategy. Pharmac staff are interested to understand the Committee's views of the available evidence for switching or sequencing biologics in AS, and any evidence for the benefits/risks of upadacitinib as a third-line treatment.

Literature Search

Pharmac staff conducted several PubMed searches on 11 April 2022 to identify any additional publications regarding upadacitinib for second-line treatment of PsA that were not identified by the supplier, further evidence for upadacitinib specifically in the third-line, and any publications regarding sequencing/switching of biologic treatments.

Table 5: Pharmac literature searches.

Search terms	Results
upadacitinib and psoriatic arthritis	• Strand et al. published patient-reported outcomes (PROs) from the SELECT-PsA 2 trial, almost all of which were nominally and significantly improved from baseline to weeks 12 and 24 with either upadacitinib dose (*P*≤0.05 for each dose vs placebo) (Rheumatol Ther. 2021;8:1827-44; **available in Appendix 1**) • Nash et al. reported that, based on pooled data from the SELECT-PsA 1 and 2 trials, upadacitinib was effective and safe whether administered as monotherapy or in combination with non-biologic DMARDs through to 24 weeks (Rheumatology (Oxford). 2021;keab905. Online ahead of print). 1342/1916 patients (70%) received combination therapy. Placebo-subtracted treatment effects (95% CI) for ACR20 at week 12 were 33.7% (24.4-43.1) for upadacitinib 15 mg monotherapy and 34.0% (27.9-40.1) for upadacitinib 15 mg combination therapy.

Search terms	Results
	• A systematic review and meta-analysis of 42 studies of JAK inhibitors (incl. 6 upadacitinib studies) reported a similar rate of venous thromboembolism events with JAK inhibitors (0.23 per 100 patient exposure years) vs placebo (0.25 per 100 patient exposure years) (Yates et al. Arthritis Rheumatol. 2021;73:779-88). • A pooled analysis of safety data from the SELECT-PsA 1 and 2 trials reported that upadacitinib 15 mg had a similar safety profile to adalimumab except for greater rates of herpes zoster and opportunistic infections with upadacitinib (Burmester et al. Rheumatol Ther. 2022;9:521-39). • A post hoc analysis of the SELECT-PsA 1 and 2 trials, and the SELECT-AXIS 1 trial in ankylosing spondylitis (AS) reported that rapid and sustained improvements in pain outcomes across several end points were shown with upadacitinib over 1 year in patients with active PsA or AS who had either received inadequate response from prior non-biologic or bDMARDs (PsA studies) or were biologic-naïve with inadequate response to NSAIDs (AS study) (McInnes et al. RMD Open. 2022;8:e002049).
upadacitinib AND psoriatic arthritis AND subsequent upadacitinib AND psoriatic arthritis AND second line upadacitinib AND psoriatic arthritis AND sequential upadacitinib AND psoriatic arthritis AND paradigm upadacitinib AND psoriatic arthritis AND algorithm upadacitinib AND psoriatic arthritis AND retreatment	Nil relevant (one consensus statement regarding treatment with JAKi was identified, but it did not aim to suggest their location in the treatment paradigm).
psoriatic arthritis AND treatment AND sequence; filtered by: publication date 2018-2022	Nil relevant (one real-world analysis of a US claims database reported 20.5% of AS patients at two years and 45.2% at 5 years had received ≥2 advanced treatments ie TNFi, non-TNFi and JAKi, but no clinical outcomes were reported. A retrospective cohort study of 2,612 Australian patients receiving TNFi for rheumatoid arthritis, PsA and AS reported similar first-line discontinuation with adalimumab/etanercept/golimumab; higher second-line discontinuation on etanercept vs golimumab (but not adalimumab vs golimumab); and longer third-line persistence with etanercept vs golimumab (no difference between adalimumab and golimumab) and that time on therapy decreased per line).

Consequences for the health system

Upadacitinib is an oral treatment that would be administered both in the community and hospital settings. It would not require injection education or administration by infusion, like other treatments for PsA. It is unclear what impact this treatment would have on health system resource use to manage the disease itself, compared with current treatments for PsA.

Suitability

The features of the medicine or medical device that impact on use

Upadacitinib is an oral treatment which can be self-administered at home. In comparison, secukinumab is given as a subcutaneous injection in either a primary or secondary care clinic (the same mode of administration as adalimumab and etanercept, although following the first dose patients may self-administer secukinumab at home) with monthly dosing after the initial dosing period. Adalimumab and etanercept are dosed more frequently – fortnightly and weekly, respectively.

Costs and Savings

PICO (Population, Intervention, Comparator, Outcome)

Table **5** below summarises Pharmac staff's interpretation of the PICO for upadacitinib for the treatment of psoriatic arthritis after inadequate response to at least one prior bDMARD.

This PICO captures key clinical contexts, helping review the proposal and frame any future economic assessment by Pharmac. We seek the Committee's advice on the content in the table below. Note that the PICO may change as clinical and other features evolve.

Table 5: PICO for upadacitinib if it were to be funded in New Zealand for patients with psoriatic arthritis after failure of one prior bDMARD.

Population	Patients with psoriatic arthritis (PsA) who received inadequate benefit from at least one prior biologic treatment Assume that patients would typically receive upadacitinib second-line (i.e. would receive upadacitinib as soon as it becomes available)
Intervention	Most common treatment sequence of: First line anti-TNF (typically adalimumab) --> Upadacitinib --> Secukinumab --> Second anti-TNF --> Supportive care

	It is also assumed that a small proportion of patients receive secukinumab first line, and may then receive upadacitinib second-line and an anti-TNF third-line -
Comparator(s) (NZ context)	Most common treatment sequence of: First line anti-TNF (typically adalimumab) --> Secukinumab --> Second anti-TNF --> supportive care Key assumption is that after failure of first-line anti-TNF, patients switch to secukinumab instead of trialling another anti-TNF A small proportion of patients (20-25%) are assumed to trial secukinumab first-line, followed by second and third-line anti-TNFs.
Outcome(s)	Improved rates of clinical response (as measured by ACR 20/50/70, swollen joint count, health assessment questionnaire (HAQ) score) vs supportive care Improved quality of life from fewer signs and symptoms of psoriatic arthritis vs supportive care Reduced radiographic progression of disease vs no treatment Based on indirect comparisons, extrapolated to assume: • Similar benefit of upadacitinib to secukinumab • Similar benefit of upadacitinib to a second anti-TNF Lower health resource utilisation (e.g. inpatient, outpatient visits) due to lower disease activity
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 patient 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.	

Costs and savings to pharmaceutical expenditure

Cost per patient

Upadacitinib is taken at a dose of 15mg once daily. The confidential net price of upadacitinib from 1 July 2022 is $S 9(2)(b) (ii) per 28 tablets; this corresponds to an annual cost of $S 9(2)(b) (ii).

For reference, the annual maintenance treatment cost of other biologics for this indication is shown below. Also shown below is the number of patients on each treatment as of 31 March 2022, and their respective market share.

Table 6: costs and market share of treatments for psoriatic arthritis

Treatment	Annual cost of maintenance treatment	Patients on treatment – 31 March 2022	Market share – at 31 March 2022
Upadacitinib	$S 9(2)(b) (ii)	-	-

Adalimumab	$S 9(2)	740	51%
Etanercept	$S 9(2)	408	28%
Secukinumab*	$S 9(2)	213	15%
Infliximab	$S 9(2)	78	5%

*This assumes that 50% of patients receive a dose of 300mg every four weeks, while 50% receive a dose of 150mg every four weeks. Note that the cost in the first year is $S 9(2)(b) due to the presence of loading doses in weeks 0, 1, 2, 3, and 4.

Estimated Incremental Total Cost of Listing

Pharmac have estimated an approximate BIA based on estimated uptake of upadacitinib, as well as estimated on how secukinumab use may grow following its listing in May 2021.

Note that the BIA should be considered indicative only, and is potentially subject to a large degree of error. A more comprehensive BIA will be conducted upon a positive clinical advice recommendation.

Key assumptions we seek the Committee's advice on include:

- Among patients who receive inadequate benefit from a first-line bDMARD, upadacitinib is likely to be used by slightly more patients than secukinumab (among patients refractory to a first anti-TNF, upadacitinib is likely to be used by 50% of patients, and secukinumab 40%). This roughly corresponds to half of the patients on upadacitinib switching from secukinumab, and half switching from a second-line anti-TNF.
- Uptake of upadacitinib is likely to be similar to that of secukinumab. While upadacitinib is more suitable, our understanding is that there was a prevalent group of patients who quickly switched to secukinumab due to inadequate response from prior treatments, and this group is unlikely to be as big for upadacitinib.

The indicative BIA is shown below.

Table 7: Indicative BIA for upadacitinib

	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**5-year NPV**
Patients treated with UPA	284	538	814	898	991	
Net impact to pharmaceutical budget	$S 9(2)	$S 9(2)	$S 9(2)	$S 9(2)	$S 9(2)	$S 9(2)
Net impact to other DHB budgets	$0.1m	$0.2m	$0.3m	$0.3m	$0.4m	$1.1m
Net impact to DHB budgets	$S 9(2)	$S 9(2)(b)	$S 9(2)	$S 9(2)	$S 9(2)	$S 9(2)(b)

Costs and savings to the rest of the health system

Pharmac staff are uncertain about whether improved disease response with upadacitinib may be associated with a reduction in health resource utilisation (HRU).

To understand the relationship between disease severity and HRU, Pharmac staff conducted an exploratory Google Scholar search using the terms “psoriatic arthritis”, “biologic”, and either “health resource utilisation” or “inpatient”. Studies reporting how HRU differed according to responders to treatment, or differed pre and post-initiation of treatment, were preferred.

The following publications were identified:

- Hur et al. Drugs Real World Outcomes 2021;9: 29-38 - this was a US publication reporting how HRU differed among patients who remained on biologic treatment, switched biologic treatments, or discontinued treatment. Patients who discontinued treatment, when compared to those who remained on their treatment in the adjusted analysis, had a higher annual number of hospitalisations (0.19 vs 0.09, ratio 2.18, 95% CI 1.59-2.98), ED visits (0.75 vs 0.33, ratio 2.27, 95% CI 1.82-2.83) and outpatient visits (27.9 vs 24.5, ratio 1.14, 95% CI 1.07-1.21).
- Sewerin et al. Arthritis Care Res 2021 (online ahead of print) – this was a German study reporting healthcare costs associated with bDMARDs in adult patients with PsA, and compared the HRU in the 12 months pre and post biologic initiation. Among all patients, the mean annual number of hospitalisations increased from 1.21 to 1.34. However, when results were analysed separately for persistent and non-persistent patients, the mean number of hospitalisations dropped for persistent patients (1.34 down to 1.12), while they increased in non-persistent patients (1.34 up to 1.73), with this difference significant between the groups. There was no difference in the mean length of stay per hospitalisation, or in the number of outpatient visits.
- Esposti et al. Biologics 2018;12: 151-8 – this was an Italian retrospective observational study assessing how HRU differed pre and post initiation of biological therapy. Among patients with psoriatic arthritis, the mean length of stay in hospital decreased from 1.3 days in the 12 months prior to initiation, to 0.5 days in the 12 months after biologic initiation.

Pharmac staff seek the Committee’s advice on whether:

- The above publications indicate biologic treatments are associated with a reduction in HRU
- Whether it would be reasonable to assume that patients who gain a response to biologics or upadacitinib in the model require fewer hospitalisations, outpatient visits, and ED visits

Cost Effectiveness (combining the Health Benefits and Costs quadrants)

The supplier has submitted a cost-minimisation analysis (CMA) comparing upadacitinib to secukinumab, based on similar efficacy between the two agents. However, a CMA is likely to be inappropriate for the following reasons:

- S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)

- The patent for secukinumab expires much sooner than upadacitinib, meaning that listing upadacitinib may pose greater long-term fiscal risk
- Listing another treatment provides another line of treatment to patients with PsA, meaning that patients are likely to remain on effective treatment for longer
- Given that secukinumab is available first-line in PsA, the comparator second-line is likely to be a combination of secukinumab and anti-TNF agents (e.g. adalimumab, etanercept), which may have different efficacy and are also S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(i)

Pharmac staff therefore intend to conduct a cost-utility analysis upon a positive clinical advice recommendation. We seek the Committee's advice on the following areas of uncertainty for the economic analysis:

- Whether biologics or upadacitinib reduce health resource utilisation (see 'Costs and savings to the rest of the health system')
- Where upadacitinib is likely to fit into the treatment algorithm

Position of upadacitinib in the treatment algorithm

As noted in the PICO table above, our understanding is that:

- Most patients receive an anti-TNF first line. However, there are likely to be some patients who receive secukinumab first-line, with 20-25% of patients initiating secukinumab over the last year not having received prior biologic treatment. We are uncertain if the number of patients receiving secukinumab first-line is likely to continue to remain small, or increase over time.
- For patients who do receive an anti-TNF first line, patients typically switch from a first-line anti-TNF to a treatment with a different mechanism of action (presently, secukinumab). Secukinumab is typically therefore used as a second-line agent, and then a second anti-TNF is currently used as a third-line agent
- Among patients who trialled an anti-TNF first line, upadacitinib would typically be used as a second-line agent, in preference to both secukinumab and a second anti-TNF.
- Among patients who trialled secukinumab first-line, upadacitinib would be preferred to an anti-TNF, due to the suitability of upadacitinib.

We seek the Committee's advice on each of the above points.

APPENDICES

Appendix 1: Key evidence from upadacitinib trials and secukinumab trials:

- Mease et al. Ann Rheum Dis. 2020;80:312-20
- Mease et al. Rheumatol Ther. 2021;8:903-19
- Strand et al. Rheumatol Ther. 2021;8:1827-44
- 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;77:890-897
- van der Heijde et al. Rheumatology (Oxford). 2020;59:1325-34
- Mease et al. RMD Open. 2021;7:e001600

Appendix 2: EXCEED trial results (McInnes et al. Lancet. 2020;395:1496-1505)

The Factors for Consideration

Factors are presented here in the order they appear in the paper, without implying any ranking or relative importance.

NEED

- The health need of the person
- The availability and suitability of existing medicines, medical devices and treatments
- The health need of family, whānau, and wider society
- The impact on the Māori health areas of focus and Māori health outcomes
- The impact on the health outcomes of population groups experiencing health disparities
- The impact on Government health priorities

HEALTH BENEFITS

- The health benefit to the person
- The health benefit to family, whānau and wider society
- Consequences for the health system

SUITABILITY

- The features of the medicine or medical device that impact on use by the person
- The features of the medicine or medical device that impact on use by family, whānau and wider society
- The features of the medicine or medical device that impact on use by the health workforce

COSTS AND SAVINGS

- Health-related costs and savings to the person
- Health-related costs and savings to the family, whānau and wider society
- Costs and savings to pharmaceutical expenditure
- Costs and savings to the rest of the health system