PTAC Pharmacology and Therapeutics Advisory Committee

Objective advice to PHARMAC

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

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Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 19 May & 20 May 2022

This meeting was held in person and via Zoom

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1. Present:

PTAC members:
Jane Thomas (Chair)
Marius Rademaker (Deputy Chair)
Alan Fraser
Brian Anderson
Bruce King
Jennifer Martin
Lisa Stamp
Matthew Strother
Rhiannon Braund
Simon Wynn Thomas
Stephen Munn

Apologies:
Elizabeth Dennett
Giles Newton Howes
Tim Stokes

2. Summary of recommendations

2.1. The following recommendation summary is in order of the discussions held at the meeting.

Pharmaceutical and Indication	Recommendation
10.4 ELX/TEZ/IVA for patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene	Medium
10.5 ELX/TEZ/IVA for patients aged six years and older who have at least one F508del mutation in the CF transmembrane conductance regulator (CFTR) gene	Medium
11.4 testosterone gel for transdermal hormone therapy	High
12.4 osimertinib for the adjuvant treatment of EGFR positive non-small cell lung cancer (NSCLC) following tumour resection	Medium
13.5 upadacitinib (Rinvoq) for the second-line treatment for adult patients with psoriatic arthritis (PsA)	Cost-neutral to secukinumab
13.6 upadacitinib (Rinvoq) for the third-line treatment for adult patients with psoriatic arthritis (PsA)	High
14.5 upadacitinib (RINVOQ) for the second-line treatment for adult patients with active ankylosing spondylitis (AS)	Cost-neutral to secukinumab
14.6 upadacitinib (RINVOQ) for the third-line treatment for adult patients with active ankylosing spondylitis (AS)	Low
15.4 bevacizumab for the first-line treatment of high-risk advanced ovarian cancer	Medium
15.6 bevacizumab for the second-line treatment of high-risk advanced ovarian cancer	Decline
16.4 sodium hypochlorite for eczema in cases with secondary bacterial infection	High

3. The role of PTAC, Specialist Advisory Committees and meeting records

3.1. This meeting record of PTAC is published in accordance with the Pharmacology and Therapeutics Advisory Committee (PTAC) Terms of Reference 2021, and Specialist Advisory Committees Terms of Reference 2021.

3.2. The PTAC Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of PTAC and Specialist Advisory Committees.

3.3. Conflicts of Interest are described and managed in accordance with sections 6.4 of both the PTAC Terms of Reference and Specialist Advisory Committee Terms of Reference.

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

Pharmac considers the recommendations provided by both PTAC and Specialist Advisory Committees when assessing applications.

4. Record of PTAC meeting held 17 February & 18 February 2022

4.1. The Committee reviewed the record of the PTAC meeting held on 17 February & 18 February 2022.

4.2. The Committee accepted the record.

5. Specialist Advisory Committee Record

Cancer Treatments Subcommittee of PTAC (CaTSoP, now CTAC)

5.1. The Committee (PTAC) reviewed the record of the Cancer Treatments Subcommittee of PTAC (CaTSoP, now the Cancer Treatments Advisory Committee (CTAC)) meeting held on 4 and 5 November 2021. The Committee noted the recommendations made by CaTSoP on funding proposals. In addition:

5.1.1. The Committee noted CaTSoP had reviewed all current funding applications related to multiple myeloma as a disease indication and considered this approach may be beneficial for other Specialist Advisory Committees.

5.1.2. The Committee noted the CaTSoP discussion regarding molecular and diagnostic testing with Te Aho o Te Kahu. The Committee noted that current access and provision of relevant testing is inconsistent across New Zealand and is often provided privately. The Committee considered that this would require a sector wide approach (Te Aho o Te Kahu, Health NZ, HSQC etc.), to centralise and provide equitable access to molecular and diagnostic testing across New Zealand.

5.1.3. The Committee considered that it could be beneficial for Pharmac to explore the possibility of having a pathologist on CTAC. The Committee also considered that it may be useful for Pharmac to consider other ways in which it could bring tumour stream expertise into the discussion for relevant items at CTAC meetings.

5.1.4. The Committee noted Pharmac's process in considering funding applications for cancer medicines in parallel with Medsafe evaluation and considered that this could result in evidence being presented at an early and incomplete state, which the Committee considered introduces challenges in making robust decisions and that this presents a growing challenge for CTAC.

Mental Health Advisory Committee

5.2. The Committee (PTAC) reviewed the record of the Mental Health Advisory Committee meeting held on 4 February 2022. The Committee noted the recommendations made by the Advisory Committee.

5.2.1. The Committee specifically noted the updated recommendation by the Advisory Committee to fund paliperidone three-monthly depot injection for schizophrenia with now a high priority, within the context of treatments in mental health. Members noted the health equity considerations of this proposal and considered that the suitability and resulting benefits of the three-monthly presentation were likely to have meaningful impacts, particularly for Māori.

5.2.2. Members noted that the Immunisation Subcommittee (now the Immunisation Advisory Committee) had previously provided advice on a proposal to fund influenza vaccine for people with serious mental health conditions and addictions. Members considered that if further advice is required in the future, the Mental Health Advisory Committee would be well placed to contribute to this.

Diabetes Subcommittee

5.3. The Committee (PTAC) noted the record of the Diabetes Subcommittee (now the Diabetes Advisory Committee) meeting held on 24 September 2021.

5.3.1. The Committee noted that the Subcommittee reviewed two funding proposals for continuous glucose monitors (CGM) and a combined insulin pump/CGM proposal.

5.3.2. The Committee noted that the Subcommittee recommended that Pharmac list the Dexcom G6 CGM system, for all people with type 1 diabetes mellitus with a high priority. The Committee noted the eligibility criteria recommended by the Subcommittee included patients with insulin-dependent diabetes secondary to cystic fibrosis, pancreatectomy, or those with permanent neonatal diabetes.

5.3.3. The Committee noted that the Subcommittee considered an application from InterMed Medical Limited for the use of the Medtronic Guardian 3 CGM system for people with type 1 diabetes. The Committee noted that the Subcommittee recommended that Pharmac decline to list the Medtronic Guardian 3 CGM system based on it being superseded by newer technology.

5.3.4. The Committee noted that the Subcommittee considered a narrower application from InterMed Medical Limited for the use of the Medtronic Guardian 4 CGM and the MiniMed 780G pump (as a part of a closed loop system) for patients currently eligible for insulin pump therapy. The Committee noted that the Subcommittee recommended that Pharmac list this with a high priority. The Committee noted that the main pathways for access to insulin pump therapy are severe unexplained hypoglycaemia, long-standing uncontrolled HbA1c, permanent neonatal diabetes, and those with a pump approval prior to 2012.

5.3.5. The Committee noted that the Subcommittee recommendations were based on; the significant health need of people with type 1 diabetes, their families/whānau and wider society, the evidence of health benefit associated with continuous glucose monitoring, and the suitability benefits associated with CGM compared with finger-prick testing.

5.3.6. The Committee noted that flash and continuous glucose monitors are funded widely in the international setting, including in Australia.

5.3.7. The Committee considered that there were security and data sovereignty issues for Pharmac to consider when contracting for diabetes technologies.

5.3.8. The Committee considered that new technologies in diabetes care presented a significant change to the treatment paradigm for people with type 1 diabetes, but that it was difficult to quantify the longer-term benefits of these technologies.

5.3.9. The Committee considered that it was unclear what criteria diabetes technologies should be evaluated against and that the quality of the evidence-base for devices differs significantly from that of pharmaceuticals.

5.3.10. Members recommended that PTAC review these proposals further, given the significant costs associated with listing CGM systems and the complexities with regards to health technology assessment.

Haematology Advisory Committee

5.4. The Committee (PTAC) reviewed the record of the of the Haematology Advisory Committee meeting held on 29 November 2021. The Committee noted the recommendations made by the Advisory Committee in relation to the funding of emicizumab.

5.4.1. The Committee noted the recommendation in relation to suggested changes to the proposed Special Authority criteria for the application for the funding of emicizumab for

patients with severe Haemophilia A without inhibitors. Members noted that with the suggested change in relation to the level of endogenous factor VIII activity (from =<1% to =<2%), that this was more appropriate to be considered as a waiver consideration rather than a change in criteria as the number of patients affected would be very small. The Committee also supported the recommendation to remove the 12-month renewal criteria.

5.4.2. The Committee noted and supported the suggested changes to the current Special Authority criteria in relation to the funding of emicizumab for people with severe Haemophilia A with inhibitors in relation to documented bleed requirements, and the removal of the requirement for 6 monthly renewals.

6. Correspondence & Matters Arising

ELX/TEZ/IVA (Trikafta) for the treatment of cystic fibrosis

Application

6.1. The Committee (PTAC) noted the draft Respiratory Advisory Committee record in relation to ELX/TEZ/IVA (Trikafta) from its April 2022 meeting, and correspondence in reply to PTAC's previous considerations of ELX/TEZ/IVA from the supplier.

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

Recommendation

6.3. The Committee **recommended** that ELX/TEZ/IVA be listed with a **medium priority** for patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, subject to the following special authority criteria (as recommended by the Respiratory Advisory Committee, April 2022; additions in **bold,** deletions in ~~strikethrough~~):

Initial application
Applications only from a respiratory specialist or paediatrician. Approvals valid without further renewal unless notified for applications meeting the following criteria:

1. Patient has been diagnosed with cystic fibrosis; and
2. Patient is 12 years of age or older; and
3. Either:
   - 3.1. Patient has two cystic fibrosis-causing mutations in the cystic fibrosis transmembrane regulator (CFTR) gene (one from each parental allele) (see note a); or
   - 3.2. Patient has a sweat chloride value of at least 60 mmol/L by quantitative pilocarpine iontophoresis or by Macroduct sweat collection system; and
4. Either:
   - 4.1. Patient has a heterozygous or homozygous F508del mutation; or
   - 4.2. Patient has a G551D mutation or other mutation responsive in vitro to elexacaftor/tezacaftor/ivacaftor (see note b); and
5. The treatment must be the sole funded CFTR modulator therapy for this condition; and
6. Treatment with elexacaftor/tezacaftor/ivacaftor must be given concomitantly with standard therapy for this condition; and
7. Applicant has experience in the management of cystic fibrosis

Notes

a) Cystic fibrosis-causing genetic mutations include F508del, G551D and other mutations listed as cystic-fibrosis causing at www.cftr2.org
b) Eligible mutations are listed on table 5 of FDA. Highlights of (Trikafta) prescribing information, June 2021

6.4. The Committee **recommended** that ELX/TEZ/IVA be listed with a **medium priority** for patients aged six years and older who have at least one F508del mutation in the CF transmembrane conductance regulator (CFTR) gene, subject to the following special authority criteria (as recommended by the Respiratory Advisory Committee, April 2022):

Initial application
Applications only from a respiratory specialist or paediatrician. Approvals valid without further renewal unless notified for applications meeting the following criteria:

1. Patient has been diagnosed with cystic fibrosis; and
2. Patient is six years of age or older; and
3. Either:
   - 3.1. Patient has two cystic fibrosis-causing mutations in the cystic fibrosis transmembrane regulator (CFTR) gene (one from each parental allele) (see note a); or
   - 3.2. Patient has a sweat chloride value of at least 60 mmol/L by quantitative pilocarpine iontophoresis or by Macroduct sweat collection system; and
4. Either:
   - 4.1. Patient has a heterozygous or homozygous F508del mutation; or
   - 4.2. Patient has a G551D mutation or other mutation responsive in vitro to elexacaftor/tezacaftor/ivacaftor (see note b); and
5. The treatment must be the sole funded CFTR modulator therapy for this condition; and
6. Treatment with elexacaftor/tezacaftor/ivacaftor must be given concomitantly with standard therapy for this condition; and
7. Applicant has experience in the management of cystic fibrosis

Notes

a) Cystic fibrosis-causing genetic mutations include F508del, G551D and other mutations listed as cystic-fibrosis causing at www.cftr2.org

b) Eligible mutations are listed on table 5 of FDA. Highlights of (Trikafta) prescribing information, June 2021

6.5. In making these recommendations, the Committee noted the Respiratory Advisory Committee responses to PTAC's previous considerations, and the supplementary information provided by the supplier and clinicians experienced in the treatment of cystic fibrosis. The Committee noted the early evidence of benefit of ELX/TEZ/IVA and acknowledged the benefit of early treatment of cystic fibrosis in preventing long term sequelae. The Committee however considered that there was significant uncertainty regarding the long-term outcomes that could be expected with ELX/TEZ/IVA and the high cost of ELX/TEZ/IVA.

Discussion

6.6. The Committee noted that it had reviewed an application for ELX/TEZ/IVA (Trikafta) for the treatment of those with cystic fibrosis (CF) at its November 2021 meeting where it recommended that ELX/TEZ/IVA be listed with a medium priority for patients aged 12 years and older who have at least one F508del mutation in the CF transmembrane conductance regulator (CFTR) gene, and deferred making a recommendation for those over six years of age and for those with mutations with in vitro evidence of benefit. The Committee noted at the time the:

6.6.1. High health need of patients with cystic fibrosis;

6.6.2. Lack of longer-term evidence of benefit from treatment with ELX/TEZ/IVA in this patient group and the insufficient evidence supporting the efficacy of ELX/TEZ/IVA for patients with CF less than 12 years of age or in patients with mutations responsive in vitro to ELX/TEZ/IVA;

6.6.3. Substantial cost of this treatment for this patient group and the impact that funding this treatment would have on the Combined Pharmaceutical Budget.

6.7. The Committee noted that the Respiratory Advisory Committee reviewed and responded to PTAC's considerations at its April 2022 meeting, and that additional information had also been provided by the supplier and clinicians specialising in the management of CF in relation to PTAC's November 2021 considerations.

6.8. The Committee noted that since its August assessment of the application for ELX/TEZ/IVA, more data had become available, which the Committee took into account when making its updated recommendations:

6.8.1. Study 107: patients with CF aged 6-11 years (Ratjen et al. J Cyst Fibros. 2021;20(Supplement 2):S265)

6.8.2. Study 116: patients with CF aged 6-11 years (Mall et al. German Cystic Fibrosis Conference (DMT). 2021;Conference abstract)

6.8.3. Study 109: patients with CF aged 12 years and over (Sutharsan et al. Lancet Respir Med. 2022;10:267-77)

Health need

6.9. The Committee noted that the Respiratory Advisory Committee clarified that the screening process for CF in New Zealand has both phenotypic and genotypic components. The Committee noted that there is population-wide newborn Guthrie screening, which detects about 90% of cases, and that patients who become symptomatic later in life would have phenotypic testing via a sweat chloride test in the first instance followed by genetic testing. The Committee noted that access to phenotypic testing was variable across centres. The Committee considered it unlikely that there would be disparities in screening and diagnosis for Māori.

Eligibility

6.10. The Committee noted the Respiratory Advisory Committee's and supplier's considerations that stopping criteria would be inappropriate for this patient population. The Committee noted that the Respiratory Advisory Committee considered it would be difficult to identify a group for which renewal criteria could apply, as it would be difficult to effectively incorporate the prevention of progression of CF versus clinical benefit from baseline, especially in younger patients or those who do not have severe disease prior to initiation of ELX/TEZ/IVA treatment. The Committee considered that cystic fibrosis was different from other conditions with more well-defined endpoints, and noted that objective clinical response varies somewhat for individuals with CF. Furthermore, the Committee noted that the Respiratory Advisory Committee considered that due to the mechanism of action, treatment with ELX/TEZ/IVA would be dictated by mutational status and therefore those patients who would not be expected to benefit would not be eligible for treatment. The Committee considered that clinicians who manage the treatment of patients with CF would act in the best interest of their patients.

6.11. The Committee also noted the Respiratory Advisory Committee considerations that there is unlikely to be any *in vivo* evidence forthcoming for those with rare mutations, due to low patient numbers, and that the *in vitro* lung epithelium model used to test CF therapeutics is well validated and accepted globally. The Committee noted that the number of patients in New Zealand without known dominant mutations is small, and considered that exclusion of patients with these rarer mutations would create a small population without access to ELX/TEZ/IVA for whom evidence of benefit would not likely be generated.

6.12. The Committee noted the Respiratory Advisory Committee's considerations that ELX/TEZ/IVA should be made available for those aged six years and over. The Committee noted that younger patients who have a percent predicted forced expiratory volume in one second (ppFEV1) lung function testing results perceived clinically as being within normal range may still have clinically significant lung disease and airway disruption, and considered

that there is no biological reason to assume that younger patients with CF would respond differently to ELX/TEZ/IVA. However, the Committee also noted that these younger patients are often pre-symptomatic in terms of lung function decline, and that measuring benefit in this population would be more difficult than with older age groups.

6.13. The Committee also noted the Respiratory Advisory Committee's considerations that early treatment with ELX/TEZ/IVA prevents development of non-pulmonary CF related illness in younger patients, but considered that there is limited evidence relating to this. The Committee also noted that there are future clinical studies planned and currently underway aiming to elucidate safety and efficacy of ELX/TEZ/IVA in patients with CF aged as young as six months.

Long term efficacy

6.14. The Committee considered that it was likely that patients currently on ivacaftor who would be eligible for ELX/TEZ/IVA would switch if it were to become available. The Committee noted an observational US registry study of more than 16,000 patients (unpublished), which reported a substantial reduction in frequency of pulmonary exacerbations on treatment. The Committee considered that this non-trial evidence supporting the benefit of ELX/TEZ/IVA to be of moderate strength given the large patient population. The Committee noted that this evidence suggested that ELX/TEZ/IVA is more effective in patients with at least one F508del mutation in the CFTR gene than other CFTR modulators in treating CF and preventing lung function decline. The Committee considered it reasonable and biologically plausible to infer that long term reductions in pulmonary exacerbations seen with ivacaftor in non-trial observational evidence could be applied to ELX/TEZ/IVA.

6.15. The Committee noted the Respiratory Advisory Committee's considerations that confining measurements of health gains to only lung function testing would likely underestimate the effectiveness and impact on quality of life of ELX/TEZ/IVA. The Committee considered it reasonable and biologically plausible to infer that long term reductions in pulmonary exacerbations seen with ivacaftor in real-world observational evidence could be applied to ELX/TEZ/IVA.

6.16. The Committee noted the Respiratory Advisory Committee's considerations regarding lung function decline and that differentiation in trajectory of disease would be somewhat dependent on baseline lung function. The Committee considered that this highlighted the benefit of treating the disease early, however re-iterated that the evidence supporting long term outcomes in patients between six and 11 years of age was particularly uncertain.

7. Testosterone gel for transdermal hormone therapy

Application

7.1. The Committee reviewed the application for testosterone gel for transdermal hormone therapy.

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

Recommendation

7.3. The Committee **recommended** that testosterone gel for transdermal hormone therapy be listed with a **high priority** as a funded replacement for testosterone undecanoate capsules following that product's discontinuation.

7.4. In making this recommendation, the Committee considered:

- The unmet health need of those who need testosterone replacement therapy and for whom testosterone transdermal patches or intramuscular injection cannot be tolerated

- The moderate- to high-strength evidence that indicates the health benefit of testosterone gel as an effective testosterone replacement therapy

- The suitability benefit of testosterone gel over the currently funded alternatives.

Discussion

Māori impact

7.5. The Committee discussed the impact of funding testosterone gel for transdermal hormone therapy on Māori health areas of focus and Māori health outcomes. Members noted the paucity of evidence available, with only one study identified (Connolly et al. BMJ Open. 2017;7), which suggested no difference in testosterone levels between Māori and non-Māori in old age but was confined to very old age groups and considered affected by selection bias. No further evidence was identified. The Committee therefore considered that the impact on Māori health outcomes to be unknown.

Background

7.6. The Committee noted that Pharmac has been informed of an upcoming discontinuation of testosterone undecanoate capsules, and that funding of this presentation is currently restricted to those who received treatment prior to 1 November 2021. The Committee noted that email correspondence with members of the Endocrinology Advisory Committee indicates that this discontinuation will result in an unmet health need; in particular, for those with a true needle phobia for injectable products or allergy to patches. The Committee noted that Pharmac has been unable to secure an ongoing supply of testosterone capsules, and that this application considers funding a gel in order to meet the health need of people requiring ongoing testosterone treatment for whom other funded options are unsuitable.

Discussion

7.7. The Committee noted that the clinical features of male hypogonadism are dependent upon the age of onset and severity of testosterone deficiency. The Committee noted that this funding application focused on adult onset (post pubertal), as Pharmac staff understood this would comprise the majority of use. The Committee noted that there would likely be some pubertal use as well for the management of adolescents experiencing delayed puberty. The Committee also considered that other patient groups requiring testosterone replacement therapy may include postmenopausal women with hypoactive sexual desire disorder and transgender individuals.

7.8. The Committee noted that the 2022 updated guidelines on male hypogonadism from the European Association of Urology state that androgen deficiency increases with age, with the major causes being: central obesity, overall poor health, and other comorbidities (eg diabetes, cardiovascular disease, chronic obstructive pulmonary disease, renal disease, cancer). The Committee noted that up to the age of 80 years, aging accounts for a low proportion of hypogonadism. The Committee noted that the incidence of symptomatic hypogonadism in men aged 40-79 years varies between 2.1-5.7%, and the overall incidence of hypogonadism has been reported to be 12.3 and 11.7 cases per 1,000 people per year. The Committee also noted that male hypogonadism is likely to be underdiagnosed and undertreated.

7.9. The Committee considered there is a high health need for patients with testosterone deficiency. The Committee noted that, regarding adult testosterone deficiency, the applicant had listed symptoms including fatigue, loss of libido, loss of body hair, muscle wasting, and weight loss, extending in some cases to osteoporosis and anaemia. The

Committee were made aware of a study that reported that those with hypogonadotropic hypogonadism have reduced health-related quality of life (HRQoL) (Kałużna et al. J Clin Med. 2021;10:2622). The Committee considered that the health need may also extend to that of the family, whānau, and partners of those with testosterone deficiency.

7.10. The Committee noted that there are a range of fully funded testosterone products currently listed on the Pharmaceutical Schedule, including patches and injections. The Committee noted that 79% of patients using testosterone products are using injections (cipionate, esters, undecanoate), 12% using undecanoate capsules, and 10% using patches. The Committee noted that the median age of patch users is 40 years and of capsule users is 64 years, and that there is a bimodal age distribution for testosterone injections with peaks at ages 20-29 and then 60-79 years.

7.11. The Committee considered that there are several suitability issues with currently available products. The Committee noted that evidence from the Scottish Medicines Consortium, supplied by the applicant, cites up to 59% of recipients of testosterone patches experienced skin rash or irritation. The Committee also considered the patches to have administration issues regarding poor adhesion of the patch to the skin. The Committee also considered that there are suitability issues with injectable preparations in the small proportion of patients with needle phobia.

7.12. The Committee noted that testosterone gel is a hydroalcoholic gel absorbed through the skin, and that the circulating testosterone mainly binds to sex hormone-binding globulin and albumin. The Committee noted that there are no Medsafe-approved testosterone gel products in New Zealand, however, Pharmac staff are seeking advice on this proposal ahead of a commercial process for a non-injectable testosterone product. The Committee noted that the recommended dosing of Testogel (testosterone gel 1%) is equivalent to 50 mg testosterone once daily, which can be adjusted in 25 mg increments up to a maximum of 100 mg testosterone daily. The Committee noted that Testogel should be administered by the patient onto clean, dry, healthy skin over both shoulders, or both arms, or abdomen (Electronic Medicines Compendium: Testogel SPC. 2021).

7.13. The Committee noted the following evidence regarding the efficacy of testosterone gel provided by the applicant:

7.13.1. Scottish Medicines Consortium: A cost effectiveness report for NHS Scotland concluding that testosterone gel offers a cost-effective transdermal treatment for adult male hypogonadism compared with testosterone patches.

7.13.2. Luthy et al. J. Nurse Pract. 2016;13(4):241-9: A review of self-administered testosterone therapy medicines in the US (efficacy, patient adherence, monthly cost, and potential side effects), which recommended testosterone gel as a third-line option, following testosterone cipionate injections (Depo-Testosterone) and testosterone patches (Androderm).

7.13.3. Williams et al. BYU ScholarsArchive. 2016;183: A review of the available testosterone products in the US, supporting the efficacy of testosterone gel products compared with other testosterone formulations.

7.14. The Committee noted the additional evidence sourced by Pharmac staff in a literature search.

- Basaria et al. N Engl J Med. 2010;363(2):109-22
- Meikle et al. BJU Int. 2004;93(6):789-95
- Kaufman et al. J Sex Med. 20129(4):1149-61
- Wang et al. J Clin Endocrinol Metab. 2000;85(8):2839-53

- Chaing et al. Int J Impot Res. 2007;19(4):411-7
- Kuhnert et al. Eur J Endocrinol. 2005;153(2):317-26
- Dias et al. Andrology. 2017;5(1):31-40
- Ripley et al. NeuroRehabilitation. 2020;46(3):355-68
- Jones et al. Diabetes Care. 2011;34(4):828-37
- Wang et al. J Clin Endocrinol Metab. 2004;89(5):2085-98
- Basaria et al. Pain. 2015;156(2):280-88
- Dobs et al. Curr Med Res Opin. 2004;20(5):729-38
- Stahlman et al. Curr Med Res Opin. 2012;28(2):271-9
- Steidle et al. J Clin Endocrinol Metab. 2003;88(6):2673-81
- Ly et al. J Clin Endocrinol Metab. 2001;86(9):4078-88

7.15. The Committee noted that testosterone gel improved sexual function and mood, increased lean mass and muscle strength (principally in the legs), and decreased fat mass in hypogonadal men, with less skin irritation and discontinuation compared with the recommended dose of the permeation-enhanced testosterone patch (Wang et al. J Clin Endocrinol Metab. 2004;89:2085-98).

7.16. The Committee was also made aware of the following studies:

7.16.1. Kałużna et al. J Clin Med. 2021;10:2622: A study reporting no differences between HRQoL scores in patients receiving hormone replacement therapy and untreated subjects.

7.16.2. Elliott et al. BMJ Open. 2017;7:e015284: A systematic review and network meta-analysis which reported, when considered as a class, improvements with testosterone replacement therapy in HRQoL, depression, erectile function, and libido when compared with placebo improved; however, when comparing the individual products directly head to head, there were few differences between the treatments.

7.16.3. Shores et al. J Am Heart Assoc. 2021;10:e020562: A study reporting that transdermal gels were not associated with an increased risk of composite cardiovascular outcome with or without prevalent cardiovascular disease (mean follow up of 4.3 years).

7.17. The Committee considered that, overall, the evidence provided was of moderate to high strength and supported the health benefit of testosterone gel as an effective testosterone replacement therapy.

7.18. The Committee considered that testosterone gel provides a suitable alternative where the currently funded patches or injection cannot be tolerated. The Committee considered that adherence to treatment would be greater in those using the gel compared to the patches. The Committee noted that there may be secondary exposure risks via transfer of gel to partners and children, however considered that education, cautious administration, and covering the application area minimises this potential risk.

7.19. The Committee considered the other potential disadvantages of testosterone gel, including dose titration issues due to the difficulty in measuring an accurate quantity of gel, and the risk of treatment abuse in those patients prescribed higher than the recommended dosage to achieve enhanced and more rapid therapeutic effects. The

Committee considered that these patterns of usage may contribute to an increased incidence of overdose and abuse. The Committee noted that the use of a product with a defined dose may mitigate some of these issues.

7.20. The Committee noted that there are currently 798 patients receiving testosterone undecanoate capsules who would be affected by the discontinuation of this product. The Committee considered that, if testosterone gel was funded as a transdermal hormone therapy, most of these patients would transition to the gel following the discontinuation of capsules.

7.21. The Committee considered that if open listed, testosterone gel would be the primary treatment of choice for patients requiring oral or transdermal testosterone therapy (ie not requiring an injectable product). The Committee noted that some patients may trial patches first, however, given the known suitability issues associated with the patches, most patients would use testosterone gel first line. The Committee considered that it would be reasonable to assume an annual discontinuation rate of 15% for patients on testosterone gel.

7.22. The Committee considered that the overall market for testosterone therapy is growing year-on-year due to its increased use in the transgender patient population. However, it considered that no additional growth over and above the background rate of growth would be expected if testosterone gel was funded.

7.23. The Committee noted Pharmac does not currently have a commercial proposal with which to assess testosterone gel compared with the currently funded treatment options. The Committee noted that, if testosterone gel was funded, and depending on pricing received, Pharmac may consider managing the financial impact with the following Special Authority criteria:

> **Special Authority for Subsidy** - Initial application
> From any relevant practitioner. Approvals valid without further renewal unless notified for applications where the patient has experienced intolerable side effects or received insufficient benefit from testosterone patches.

7.24. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for testosterone gel if it were to be funded in New Zealand for transdermal hormone therapy. 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 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	Mostly post-pubertal patients with confirmed testosterone deficiency, requiring testosterone therapy, with small numbers for other indications.
Intervention	Testosterone gel, 5 mg testosterone once daily. If testosterone gel proved effective and well-tolerated, testosterone gel may be used as a lifelong hormone therapy.
Comparator(s) (NZ context)	Testosterone transdermal patches (2.5-7.5 mg once per 24 hours), some patients may also switch from testosterone injections.
Outcome(s)	Non-inferiority to transdermal patches for the treatment of testosterone deficiency regarding: • Achievement of serum testosterone levels to within the reference range • Improved sexual function and mood • Increased lean mass • Decreased risk of rash or skin irritation compared to transdermal patches • Improved adherence to treatment (compared with patches)
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.	

8. Osimertinib for the adjuvant treatment of EGFR positive non-small cell lung cancer following tumour resection

Application

8.1. The Committee reviewed the supplier application for osimertinib for the adjuvant treatment of EGFR positive non-small cell lung cancer (NSCLC) following tumour resection.

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

Recommendation

8.3. The Committee **recommended** that osimertinib for the adjuvant treatment of EGFR positive non-small cell lung cancer (NSCLC) following tumour resection be listed with a **medium priority** subject to the following Special Authority criteria:

OSIMERTINIB

Special Authority for Subsidy – Retail Pharmacy - Specialist

Initial application – (NSCLC – adjuvant following resection) only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:

All of the following:

1. Treatment is to be used as an adjuvant therapy following surgical resection of Stage IB to Stage IIIA non-squamous Non-Small Cell Lung Cancer (NSCLC); and
2. There is documentation confirming that the disease expresses activating mutations of EGFR tyrosine kinase; and
3. Patient has a ECOG Performance status of 0 or 1; and
4. Patient has not received prior neo-adjuvant treatment with a tyrosine kinase inhibitor; and
5. Patient has not received perioperative or postoperative radiation therapy.

Renewal - only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:

1. The treatment remains clinically appropriate and the patient is benefitting from treatment; and
2. Radiological assessment indicates NSCLC has not progressed; and;
3. Treatment with osimertinib to cease upon signs of disease progression; and
4. Total continuous treatment duration must not exceed three years.

8.4. In making its recommendation, the Committee noted the significant disease-free survival benefit for patients treated with osimertinib, the convenience and suitability of having an oral treatment, and the high unmet health need in the NSCLC patient population. The Committee also considered the immature overall survival results reported in the pivotal trial.

8.5. The Committee also recommended advice be sought from the Cancer Treatments Advisory Committee (CTAC) regarding:

8.5.1. the proportion of patients who are eligible for surgical resection who are stage IB to IIIA

8.5.2. the proportion of patients who receive platinum-based chemotherapy as adjuvant therapy following resection

8.5.3. the appropriateness of continuing treatment with osimertinib for longer than three years if there is no disease progression

8.5.4. whether NICE's assumption, that patients are cured if they do not progress 8 years after treatment initiation, is reasonable

8.5.5. the likelihood that osimertinib would be used in combination with chemotherapy in the adjuvant setting, given limited evidence of benefit for combining first and second generation TKIs with chemotherapy in other treatment lines

8.5.6. whether prevalent patient number estimates of 10 patients in the first year of funding and 18 patients per year at year five are reasonable.

Discussion

Māori impact

8.6. The Committee noted that Māori are disproportionately impacted by lung cancer, compared with non-Māori, and that lung cancer develops earlier in Māori compared with non-Māori.

8.7. The Committee noted that Māori had the lowest overall survival of all ethnic groups, with 37.7% alive one year after diagnosis, 21.6% two years after diagnosis and 17.5% three years after diagnosis.

8.8. The Committee noted the study by Aye et al. which reported that standardised incidence ratios of EGFRm positive NSCLC were higher for Pacific people, Asian people, and Māori than Europeans; relative rate of 3.47, 3.35, 2.02, and 1 respectively (Aye et al. PLoS One. 2021;16:e0251357).

8.9. The Committee noted that this application is for a specific sub-group of patients with EGFR-positive NSCLC following tumour resection. The Committee considered that, were osimertinib to be funded in this setting, there may be reduced benefit for Māori due to the lower rates of surgery with curative intent amongst the Māori patient population.

8.10. The Committee noted the lack of clinical trial evidence for the use of osimertinib specifically in Māori but had no reason to believe efficacy would be any different to that reported in clinical trials of other ethnic groups.

Discussion

8.11. The Committee noted that NSCLC is generally grouped into 5 stages (American Joint Committee on Cancer (AJCC)), and that the stages for the requested indication are stages IB, II, and IIIA. The Committee noted that tumours in these stages have not yet metastasised to distal organs and are therefore often resectable. The Committee noted

that disease-free survival for NSCLC is strongly correlated with disease stage, with patients diagnosed at an earlier stage having a longer disease-free survival.

8.12. The Committee noted that the health need of patients with EGFRm positive NSCLC was previously well described by PTAC in August 2020 and CaTSoP in April 2021, where osimertinib was assessed as treatment for NSCLC in the first and second-line settings.

8.13. The Committee noted that in 2019, a total of 2,344 lung cancer registrations were recorded in New Zealand, with an age standardised rate of 27.6 per 100,000 (Ministry of Health, 2021). The Committee noted that patients with resectable NSCLC comprise 20-25% of the total lung cancer population globally.

8.14. The Committee noted that Māori are disproportionately impacted by lung cancer, compared with non-Māori: In 2019, the incidence of lung cancer for Māori was 68.4 per 100,000. The Committee also noted that lung cancer develops earlier in Māori compared with non-Māori, with incidence rates peaking at age 70-74 years for Māori (730.3 per 100,000) versus age 80-84 years for non-Māori (256.9 per 100,000) (Ministry of Health, 2019).

8.15. The Committee noted that, according to the Te Aho o Te Kahu report, Māori and Pacific peoples had low curative resection rates compared with other ethnic groups (12.2% for Pacific people, 13.4% for Māori, 17.2% for NZ European/Other, and 25.0% for Asian people). The Committee noted that it was unclear why this may be but considered that lower curative resection rates in the Māori patient population may be due to later presentation of NSCLC, or lower referral to, or suitability for, curative resection. The Committee noted that Māori also had the lowest overall survival of all ethnic groups. The Committee recommended advice be sought from CTAC regarding the proportion of patients who are eligible for surgical resection who are stage IB to IIIA.

8.16. The Committee noted that two first-generation tyrosine kinase inhibitors (TKIs), erlotinib and gefitinib are currently funded for the first line treatment of locally advanced or metastatic, unresectable, non-squamous EGFRm positive NSCLC and that both are oral tablet formulations taken once daily. The Committee noted that following progression on erlotinib or gefitinib, patients may receive platinum-based doublet chemotherapy and then after subsequent progression, receive treatment with docetaxel. The Committee noted that the 5-year absolute overall survival benefit for patients treated with adjuvant chemotherapy is 5.4% (hazard ratio 0.89; 95% CI 0.82 to 0.96), and that the five-year hazard ratio for disease free survival benefit is 0.84 (95% CI 0.78 to 0.91; Zhang SS. Lung Cancer (Auckl) 2022;13:23-31).

8.17. The Committee noted that although surgery is an available treatment option for patients with early-stage NSCLC, a recent Te Aho o Te Kahu report indicated that in New Zealand, between 2015 – 2018, only 16.7% of NSCLC patients underwent curative surgical resection, increasing to 17.2% of those with NSCLC and a prior pathological diagnosis, compared to the 20-25% standard globally. (Te Aho o Te Kahu. 2021. Lung Cancer Quality Improvement Monitoring Report 2021). The Committee noted that there are currently no funded targeted options for adjuvant therapy following resection of EGFRm positive NSCLC, and that patients currently receive platinum-based chemotherapy if deemed necessary or appropriate following surgery, followed by docetaxel upon progression. The Committee noted that if osimertinib were offered as adjuvant treatment, this would be as monotherapy, as there is no evidence that using it in combination with chemotherapy provides additional benefit. The Committee noted that the 2021 Te Aho o Te Kahu report indicated that of those diagnosed with NSCLC, systemic anti-cancer therapy was received by 32.0% of Māori patients, 37.7% of Pacific patients, 42.4% of Asian patients, and 27.0% of NZ European/Other patients. The Committee recommended advice be sought from CTAC regarding the proportion of patients who receive platinum-based chemotherapy as adjuvant therapy following resection.

8.18. The Committee noted that osimertinib is an orally administered third generation TKI; a selective and irreversible inhibitor of Epidermal Growth Factor Receptors (EGFRs) harbouring single (L858R or del746-750) or double (L858R/T790M or del746-750/T790M) mutations. The Committee noted that osimertinib has been previously considered by PTAC and CaTSoP for two indications; first line treatment of patients with locally advanced/metastatic EGFRm NSCLC (PTAC – August 2020 recommended funding if cost-neutral to current first-line pharmaceuticals in this indication; CaTSoP – April 2021 recommended funding with a high priority), and second line treatment of patients with locally advanced/metastatic EGFRm NSCLC (PTAC – 21 August 2020 deferred making a funding recommendation pending publication of overall survival results; CaTSoP – April 2021 recommended funding with a high priority after prior EGFR tyrosine kinase inhibitor (TKI) therapy).

8.19. The Committee noted that osimertinib is Medsafe approved for the adjuvant treatment of EFGR-positive NSCLC following resection and that the recommended dose in the adjuvant setting is 80 mg/day (reduced to 40 mg/day if needed) for three years or until disease progression. The Committee noted that osimertinib for the adjuvant treatment of NSCLC following resection has been recommended by health technology assessment agencies in Canada (CADTH), Scotland (SMC) and England/Wales (NICE).

8.20. The Committee noted the randomised, double-blind, placebo-controlled phase III ADAURA trial, which provided the key evidence for the use of osimertinib as adjuvant treatment following resection of EGFR-positive NSCLC (Wu et al. N Engl J Med. 2020;282:1711-23). The Committee noted that patients were randomised 1:1 to receive either osimertinib 80 mg once daily (n=339) or placebo (n=343) for three years. The Committee noted that the primary endpoint was disease-free survival in stage II to IIIA NSCLC, and that the secondary endpoint was disease-free survival in stage IB to IIIA patients.

8.20.1. The Committee noted that the stage II-IIIA patients had a disease-free survival at 24 months of 90% with osimertinib (95% CI 84 to 93) compared to 44% with placebo (95% CI 37 to 51), with a hazard ratio (HR) for recurrence or death of 0.17 (99.06% CI 0.11 to 0.26). The Committee noted that for the overall population the disease-free survival at 24 months was 89% in the osimertinib group (95% CI 85 to 92) compared to 52% with placebo (95% CI 46 to 58), with an HR for recurrence or death of 0.20 (99.12% CI 0.14 to 0.30). The Committee noted that the overall survival data for the ADAURA trial was immature, but that double the number of patients in the placebo arm compared to the osimertinib treatment arm had died at 24 months. The Committee also noted that there were no new safety concerns reported.

8.20.2. The Committee noted that subgroup analysis reported that all subgroups favoured osimertinib for HRs for disease recurrence or death, including disease stage, EGFR mutation, age, and race. The Committee also noted that the probability of CNS disease-free survival was significantly better for the osimertinib treated group compared to the placebo group (HR 0.18; 95% CI 0.10 to 0.33). The Committee considered it was unclear how the CNS disease-free survival affected the overall survival but considered that any impact on CNS disease free survival was important. The Committee noted that osimertinib is known to have better blood-brain-barrier penetration than other TKIs. The Committee noted that osimertinib had a higher incidence of grade three adverse events compared to placebo but considered that these were all in the scope of general oncological practice.

8.21. The Committee noted separately published health-related quality of life (HRQoL) results from the ADAURA trial (Majem et al. Clin Cancer Res. 2022; Online ahead of print). The Committee noted that HRQoL was measured using the Short Form-36 (SF-36) health survey at baseline, 12, and 24 weeks, then every 24 weeks until recurrence or treatment completion/discontinuation. The Committee noted that there were no clinically meaningful differences in HRQoL reported between treatment arms. The Committee noted that the time to deterioration for both mental and physical in the HRQoL study was the same between treatment arms and considered that this reflected patients' relatively good health

status at early-stage disease. The Committee noted that patients in the placebo group were switched to the osimertinib treatment arm upon recurrence and considered that this may be why the HRQoL results between the groups were so similar. The Committee considered that the effect of patients crossing treatment groups may also affected the overall survival results in ADAURA.

8.22. The Committee considered that the quality of the ADAURA trial was good but noted that the overall survival data was immature and did not indicate a strong overall survival benefit to date, noting also the potential effects of patient cross-over on the results.

8.23. The Committee noted that there is evidence for the use of first and second generation TKIs in the adjuvant treatment setting, which shows in general a significant benefit of TKIs versus chemotherapy with regard to disease-free survival, but generally no significant benefit in overall survival if any.

8.23.1. The EVAN trial (Yue et al. Lancet Respir Med. 2018;6:863-73) compared erlotinib with cisplatin with vinorelbine as adjuvant therapy following resection in patients with stage IIIA EFGR-positive NSCLC. The median disease-free survival in the erlotinib treatment group was 42.4 months versus 21.2 months in the cisplatin treatment arm (HR 0.327, P < 0.0063). The five-year overall survival was 84.8% with erlotinib versus 51.1% in the cisplatin treatment group (HR 0.318, P = 0.0015).

8.23.2. The ADJUVANT/CTONG1104 trial (Zhong et al. Lancet Oncol. 2018;19:139-48) compared gefitinib with vinorelbine plus cisplatin as adjuvant treatment following recession of stage II-IIIA EGFR positive NSCLC. The median disease-free survival was 30.8 months in the gefitinib group versus 19.8 months in the cisplatin treated group (HR 0.56, P = 0.001). The 5-year overall survival was 53.2% in the gefitinib treated group versus 51.2% in the cisplatin treated group (HR 0.92, P = 0.674).

8.23.3. The EVIDENCE trial (He et al. Lancet Med Rispir. 2021;9:1021-9) compared icotinib with chemotherapy adjuvant treatment following resection for stage II-IIIA EGFR-positive NSCLC. The median disease-free survival was 47.0 months in the icotinib treatment arm versus 19.8 months in the chemotherapy treated arm (HR 0.36, P < 0.0001). The three-year disease-free survival was 63.9% versus 32.5%. Overall survival data were immature, with improvements in OS not reaching statistical significance (with 14 (9%) deaths in the icotinib group, 14 (11%) deaths in the chemotherapy group, HR 0·91 (95% CI 0·42-1·94) in the full analysis set).

8.23.4. The IMPACT trial (Tada et al. J Clin Oncol. 2022;40:231-41) compared gefitinib to cisplatin with vinorelbine for patients with resected stage II-IIIA EGFR-positive NSCLC. The median disease-free survival was 35.9 months in the gefitinib treatment arm versus 25.1 months in the cisplatin treatment arm (HR 0.92, P = 0.63;). The five-year overall survival was 78.0% in the gefitinib arm versus 74.6% in the cisplatin treatment arm (HR 1.03, P = 0.89).

8.24. The Committee also noted the ALCHEMIST trial (ClinicalTrials.gov Identifier: NCT02193282), an ongoing phase III trial comparing treatment with erlotinib hydrochloride with placebo for two years in completely resected stage IB-IIIA EGFR-positive NSCLC.

8.25. The Committee noted a comparison for first generation TKIs in the treatment of 588 patients with EFGR positive NSCLC as adjuvant therapy following resection (He et al. Transl Lung Cancer Res. 2021;10:4120-9). The Committee noted that the median disease-free survival results were 36.1 months (95% CI 23.9 to 49.4), 42.8 months (95% CI 29.6 to 97.8) and 32.5 months (95% CI 23.9 to 49.4) for gefitinib, erlotinib, and icotinib, respectively.

8.26. The Committee noted a meta-analysis investigating the efficacy and safety of adjuvant EGFR TKIs compared to placebo or chemotherapy for resected NSCLC (Zhao et al. BMC Cancer. 2022;22:328). The Committee noted that nine randomised controlled trials were included, totalling 3098 patients. The Committee noted that the meta-analysis reported that

adjuvant EGFR-TKIs could significantly prolong disease-free survival in patient with resected NSCLC with EGFR mutations (HR 0.46; 95% CI 0.29 to 0.72) but had no statistically significant impact on overall survival (HR 0.87; 95% CI 0.69 to 1.11), which may reflect cross-over in the various trials. The Committee noted that subgroup analyses indicated that adjuvant EGFR-TKIs were superior in regard to disease-free survival in most subgroups, including smoking status, EGFR mutations type, gender, age, ECOG performance status and adenocarcinoma. The Committee also noted that osimertinib resulted in decreased brain recurrence than first generation of EGFR-TKIs, and that high grade adverse events including diarrhoea and rash increased following TKI treatment.

8.27. The Committee noted the double-blind phase III FLAURA trial (Soria et al. N Engl J Med. 2018;378:113-25), which compared osimertinib to gefitinib and erlotinib for the treatment of patients with previously untreated, EGFR–positive advanced NSCLC (a wider indication than post-curative resection). The Committee noted that median progression-free survival was longer with osimertinib compared to the first generation TKIs (18.9 months vs. 10.2 months; HR for disease progression or death 0.46; 95% CI 0.37 to 0.57; P<0.001).

8.27.1. The Committee noted that the 18-month survival results were immature, but reported 83% (95% CI 78 to 87) with osimertinib and 71% (95% CI 65 to 76) with standard EGFR-TKIs (HR for death 0.63; 95% CI 0.45 to 0.88; P=0.007).

8.27.2. The Committee noted a longer follow-up of the FLAURA study (Ramalingam et al. N Engl J Med. 2020;382:41-50) which indicated that the median overall survival was 38.6 months (95% CI 34.5 to 41.8) in the osimertinib group and 31.8 months (95% CI 26.6 to 36.0) in the comparator group (HR for death 0.80; 95.05% CI 0.64 to 1.00; P = 0.046). The Committee also noted that at three years 79 of 279 patients (28%) in the osimertinib group and 26 of 277 (9%) in the comparator group were continuing to receive a trial regimen.

8.27.3. The Committee considered that although this study was not in the adjuvant treatment setting, advice should be sought from CTAC regarding the appropriateness of continuing treatment with osimertinib for longer than three years if there is no disease progression, based on the number of patients still on treatment at three years in the FLAURA trial. The Committee noted that NICE assumes that patients are cured if they do not progress 8 years after treatment initiation and considered that this was a reasonable assumption, but recommended advice be sought from CTAC regarding this.

8.28. The Committee noted the 2022 report by Te Aho o Te Kahu (Cancer Control Agency: Mārama ana ki te Āputa: he tātari i te wāteatanga o ngā rongoā mate pukupuku i Aotearoa - Understanding the Gap: an analysis of the availability of cancer medicines in Aotearoa), which identified and outlined gaps in treatment options for New Zealanders with a range of cancers, including NSCLC. The Committee noted that the report included osimertinib for first- and second-line treatment of EGFR-positive NSCLC and identified a gap for these indications where osimertinib may provide substantial clinical benefit. The Committee noted that the Te Aho o Te Kahu 2022 report did not include consideration of osimertinib in the adjuvant setting for patients post-resection.

8.29. The Committee considered the prevalent patient number estimates of 10 patients in the first year of funding, increasing to 18 patients per year after five years to be reasonable, but considered that advice be sought from CTAC to confirm patient numbers.

8.30. The Committee noted a cost-effectiveness study of osimertinib compared to placebo for patients with resected EGFR-positive NSCLC from the ADAURA trial which reported that a 30% improvement in overall survival rate would be necessary for osimertinib to be cost effective (Lemmon et al. Oncologist. 2022; 27:407-13).

8.31. The Committee noted that access to EGFR testing in New Zealand is variable across the country, but that it is already performed routinely following lung cancer resection. The Committee also considered that funding osimertinib in the adjuvant setting would not impact on the use of currently funded erlotinib or gefitinib in the metastatic NSCLC setting.

The Committee considered it unlikely that osimertinib would be used in combination with chemotherapy in the adjuvant setting, as there is limited evidence of benefit for combining first and second generation TKIs with chemotherapy in other treatment lines. The Committee recommended that advice be sought from CTAC regarding this.

8.32. The Committee considered that it would be beneficial to review the landscape of first, second and third generation TKIs in the treatment of EGFR-positive NSCLC, and to revisit previous recommendations for these agents, including osimertinib, where there is new information available since previous considerations.

8.33. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for osimertinib if it were to be funded in New Zealand for the adjuvant treatment following resection of EGFR-positive NSCLC. 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 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	Patients with EGFR mutation NSCLC who have had tumour resection.
Intervention	Osimertinib, 80mg (tablet) once per day until disease progression or max duration of 3 years (whichever is earlier). On progression: 1) Platinum based chemotherapy Docetaxel
Comparator(s) (NZ context)	Platinum based chemotherapy On progression Docetaxel
Outcome(s)	Longer disease-free survival (median disease-free survival was 27.5 months for placebo and not reached for Osimertinib). Overall survival is expected to be longer, however data is too immature to draw conclusions from.
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.	

9. 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]

Application

9.1. The Committee reviewed the 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).

9.2. The Committee noted that Pharmac staff also sought 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.

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

Recommendation

9.4. The Committee **recommended** that upadacitinib be listed in the Pharmaceutical Schedule for the second-line treatment of PsA only if **cost-neutral** to secukinumab, subject to Special Authority criteria.

9.4.1. In making this recommendation, the Committee considered:

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

9.4.1.2. The suitability of an oral treatment for PsA, including the potential impact this formulation may have on health outcomes for Māori with PsA, in particular.

9.5. The Committee **recommended** that upadacitinib be listed in the Pharmaceutical Schedule for the third-line treatment of PsA with a **high priority**, subject to Special Authority criteria.

9.5.1. In making this recommendation, the Committee considered that:

9.5.1.1. Patients with PsA have limited effective treatment options after the use of currently funded biologic treatments and an additional option for third-line treatment would be beneficial for this chronic disease

9.5.1.2. The suitability of an oral treatment for PsA, including the potential impact this formulation may have on health outcomes for Māori with PsA, in particular.

9.5.1.3. There was weak to moderate strength evidence for a benefit from upadacitinib in patients who received treatment with two prior biologic DMARDs

9.5.1.4. Upadacitinib appears to provide a benefit when used in later lines in PsA, however, like bDMARDs, the likelihood of benefit is typically smaller in later lines of treatment as opposed to use in bDMARD-naïve patients.

9.6. The Committee considered that Pharmac should 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 patients 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 patients who would switch to upadacitinib second-line and third-line upon listing and what size that group might be
- Special Authority criteria for upadacitinib for second-line and third-line treatment of PsA.

Discussion

Māori impact

9.7. The Committee considered that there was no specific evidence of a disproportionate impact from PsA on Māori. The Committee considered that the suitability of upadacitinib as

an oral treatment would be of benefit especially to Māori, who may find it more suitable and accessible than alternative treatments that are injected subcutaneously.

Discussion

9.8. The Committee noted that psoriatic arthritis (PsA) is a systemic, heterogenous inflammatory musculoskeletal disease which occurs in about 20-30% of people with psoriasis (a skin disease occurring in 3% of adults and <1% of children). The Committee noted that major manifestations of PsA include inflammatory arthropathy and enthesitis usually associated with skin manifestations. 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 noted that PsA is associated with higher mortality and considered that the risk of mortality in PsA is greater for patients more active disease.

9.9. The Committee considered that PsA impacts on a patient's function/activities and employment, which in turn impacts their family and whānau, particularly as the disease progresses and the individual's pain and mobility worsen. The Committee considered that there was reasonable evidence for the health needs of patients with PsA, however, that there was no specific evidence of a disproportionate impact from PsA on Māori, Pacific peoples, or other groups experiencing health disparities.

9.10. The Committee noted that the aim of treatment for PsA is to reduce the functional and systemic impact of the disease. The Committee noted that there is no agreed New Zealand-specific treatment paradigm for PsA, and was made aware of recent international guidelines from 2018 (Singh et al. Arthritis Rheumatol. 2019;71:5-32) and 2020 (Ogdie et al. Rheumatology (Oxford). 2020;59(Suppl_1):i37-i46) which include treatment guidelines and recommendations from the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR). The Committee was made aware that the sequence of treatments for PsA in these guidelines commences with physical therapies followed by non-steroidal anti-inflammatories according to a 'treat to target' principle, and that following this treatment may be escalated to the use of conventional disease-modifying antirheumatic drugs (DMARDs) or to a biologic DMARD (bDMARD). The Committee noted that funded bDMARD options include tumour necrosis factor inhibitors (TNFi, ie adalimumab or etanercept) or an interleukin-17 inhibitor (IL17i) such as secukinumab, and that these may also be used in combination with a conventional DMARD. The Committee was made aware that subsequent options available internationally with different mechanisms of action to TNFi and IL17i may include upadacitinib, tofacitinib, abatacept or guselkumab.

9.11. The Committee considered that adalimumab would be the most common first-line bDMARD in New Zealand due to its benefits for skin and joint disease and considered that the disease-related threshold to access funded bDMARDs in New Zealand is high and would include patients with severe and erosive disease (the Special Authority criteria for adalimumab currently requiring 15 swollen or four major joints with persistent symptoms of poorly controlled active disease to be eligible). The Committee noted that secukinumab was funded in 2021 for PsA and that Pharmac's Special Authority data reports 20-25% of secukinumab patients with PsA had not had a prior biologic. The Committee considered this could be due to patients who received adalimumab in the past having a long delay before starting secukinumab. The Committee also considered that first-line use of secukinumab would be unlikely to increase over time given the preference for a first-line anti-TNF and the residual uncertainty about the optimal treatment sequencing in PsA. The Committee considered that the use of secukinumab first-line would be unlikely to increase, although considered that Pharmac should seek the Rheumatology Advisory Committee's views on secukinumab first-line use. The Committee considered that some patients would receive treatment with a TNFi then proceed to secukinumab second-line and then receive another TNFi in the third line, although some might receive a different TNFi in the second-line and then receive secukinumab third line, where there is a preference to treat within the

same class initially. The Committee considered there was uncertainty in the current treatment paradigm and that Pharmac should seek advice from Rheumatology Advisory Committee regarding this.

9.12. The Committee considered that funded biologic DMARDs (bDMARDs) treatments such as adalimumab, etanercept, and secukinumab have a time-limited benefit with treatments tending to be associated with a loss of clinical benefit at a predictable rate. The Committee considered that, as a consequence, patients transition to another treatment option either within the same class or with a different mechanism of action, although noting that response rates diminish with each subsequent bDMARD. The Committee considered that there is a greater unmet health need for another third-line treatment than there is for another second-line treatment in PsA, considering the available funded options and benefits that may be gained from them in the second-line versus third-line setting.

9.13. The Committee considered that there is high persistence in New Zealand on TNFi and that some patients may remain on treatment, despite not experiencing the 50% reduction in swollen joints required to meet the renewal criteria for bDMARDs, if they have no other funded treatment options. Members considered that some patients and their clinicians prefer not to change the treatment but rather accept small benefits with the same ongoing treatment, and that it is common for patients and clinicians to try to obtain as much benefit as they can from a particular treatment before opting to switch. The Committee considered that Pharmac should also seek the Rheumatology Advisory Committee's view on whether patients with PsA who receive smaller benefits from treatment (eg a 20% improvement) would remain on their treatment.

9.14. The Committee noted that upadacitinib is an oral, selective Janus Kinase-1 (JAK1) inhibitor (JAKi) and is a targeted synthetic treatment. The Committee considered that, based on the available evidence, the fact that upadacitinib is a targeted synthetic is unlikely to make a difference to likely response rates compared with currently funded bDMARDs for PsA. Members considered that there does not appear to be an overall JAKi class effect yet identified but considered that subclasses of JAKi exist and that these types have similar effects and subtle differences depending on the indication. The Committee noted that upadacitinib is Medsafe-approved for the treatment of active PsA, in adult patients for whom one or more DMARDs have not provided an adequate response or are not tolerated (used as monotherapy or in combination with a non-biological DMARD). The Committee noted that the proposed dosing for upadacitinib in PsA is 15mg daily, not 30mg, as the higher dose was not pursued by the supplier due to toxicity.

9.15. The Committee noted that the application proposed upadacitinib be funded as a second or subsequent treatment in the paradigm for PsA following the use of bDMARDS (adalimumab or etanercept) and that the comparator proposed was secukinumab.

9.16. The Committee noted that upadacitinib has been recommended for funding in Australia (PBAC, 2021) and in Canada (CADTH, 2021) for patients with PsA who, in effect, have not experienced an adequate response to conventional DMARDs, the Canadian recommendation being subject to cost neutrality with biological DMARDs or targeted synthetic DMARDs; and has been recommended for funding in England and Wales (NICE, 2022) for patients with PsA who have had two conventional DMARDs and at least one biological DMARD, or for whom TNFi are contraindicated. Members noted that upadacitinib in the first line did not meet the NICE cost-utility threshold, however, in the second line it was above the £20,000 threshold under which NICE generally considers technologies cost-effective.

9.17. The Committee noted the evidence for upadacitinib in the target population comes from the randomised (2:2:1:1), placebo- controlled, double- blind, phase 3 SELECT PsA 2 trial in 642 adult patients with active PsA, ≥3 each of swollen and tender joints, and prior inadequate response from or intolerance to ≥1 bDMARD (Mease et al. Ann Rheum Dis. 2020;80:312-20). The Committee noted that participants received once daily treatment with either upadacitinib 15 mg, upadacitinib 30 mg, placebo followed by upadacitinib 15 mg at

week 24, or placebo followed by upadacitinib 30 mg at week 24. The Committee noted the characteristics of trial participants and considered that the relevant New Zealand patient population would be similar. The Committee noted that about one third of the trial population had received two prior bDMARDs and therefore the trial represented evidence of both second-line and third-line use, although the trial outcomes were not reported stratified according to the number of prior lines.

9.17.1. The Committee noted that the primary endpoint of SELECT PsA 2, the proportion of patients with improvement in American College of Rheumatology (ACR) 20 response at week 12, was 56.9% with upadacitinib 15 mg, 63.8% with upadacitinib 30 mg and 24.1% with placebo (P<0.001 for both upadacitinib arms vs placebo). The Committee noted that ACR50 at week 12 was 31.8% with upadacitinib 15 mg, 37.6% with upadacitinib 30 mg and 4.7% with placebo, and AR70 at week 12 was 8.5% with upadacitinib 15 mg, 16.5% with upadacitinib 30 mg and 0.5% with placebo (P≤0.05 for each upadacitinib dose vs placebo). The Committee considered that there was evidence of a benefit of upadacitinib compared with placebo and that the two upadacitinib doses had similar efficacy to each other. Members considered that the proportions receiving ACR20/50/70 responses represented a typical spread of these outcomes of therapy in this disease. The Committee considered that the ACR20/50/70 are reported to correlate with health-related quality of life and productivity measures, and members considered that patients may experience a greater benefit than is indicated by the ACR20 result alone.

9.17.2. The Committee noted that the proportions of patients achieving a 75% improvement in the Psoriasis Area Severity Index (PASI75) at week 24 in SELECT PsA 2 was 53.8% with upadacitinib 15 mg, 62.6% with upadacitinib 30 mg and 19.1% with placebo (P<0.05 for each upadacitinib dose vs placebo). Members considered that the PASI75/90/100 scores were spread in a similar manner to the ACR20/50/70 responses.

9.17.3. The Committee noted that the proportion of patients achieving minimal disease activity (MDA) at week 24 in SELECT PsA 2 was 25.1% with upadacitinib 15 mg, 28.9% with upadacitinib 30 mg and 2.8% with placebo (P<0.05 for each upadacitinib dose vs placebo). The Committee noted that MDA is reported to correlate with outcomes including radiologic progression, quality of life and productivity measures. Members considered that MDA may be a more rigorous, useful and desirable measure than ACR20 from a patient perspective, and considered that MDA represents a state of almost full health.

9.17.4. The Committee noted that the change from baseline in Disease Activity in Psoriatic Arthritis (DAPSA) score at week 24 in SELECT PsA 2 was -33.4 with upadacitinib 15 mg, -36.6 with upadacitinib 30 mg and -14.3 with placebo (P≤0.05 for each upadacitinib dose vs placebo). The Committee noted that the DAPSA is a composite score that uses clinical and non-clinical measures.

9.18. The Committee noted that at 56 weeks in SELECT PsA 2 (Mease et al. Rheumatol Ther. 2021;8:903-19), after the placebo groups had crossed over to upadacitinib 15mg or 30mg, the proportion of patients achieving ACR20/50/70 was 59.7%/40.8%/24.2% with upadacitinib 15mg and 59.2%/38.5%/26.6% with upadacitinib 30mg. The Committee noted that about half of the patients were still receiving upadacitinib at 56 weeks and considered that the effect of upadacitinib vs placebo seen at 24 weeks was sustained to 56 weeks.

9.18.1. The Committee noted that at 56 weeks the main difference in adverse events (AEs) in SELECT PsA 2 from what was reported at 24 weeks was the risk of infection in both the upadacitinib 15mg and 30mg groups, although considered that an increased risk of infection is not uncommon with treatments for PsA. The Committee noted that the higher dose (30mg) was not pursued by the supplier for PsA due to its association with an increased incidence of AEs. Members noted that AEs in SELECT PsA 2 were reported according to a log scale, used Poisson regression, and that the point estimates were not centrally positioned. Members considered that infections with herpes simplex would be manageable, however, that a recombinant vaccine for herpes zoster would be desirable given that live vaccines are contraindicated for patients receiving upadacitinib.

9.19. The Committee noted that another JAK inhibitor, tofacitinib, has an FDA black box warning regarding the risk of myocardial infarction, cerebrovascular events, cancer, blood clots or death. The Committee considered that the 56-week safety data for upadacitinib in PsA was insufficient to fully determine its potential medium-term risks. However, the Committee noted that there is growing evidence for the use of JAK inhibitors, which share some subclass effects, for other diseases and noted that preclinical evidence suggests upadacitinib's selective inhibition of JAK1 may impact on its safety profile compared with tofacitinib, which inhibits JAK2/3.

9.20. The Committee considered that there is no evidence to indicate whether or not upadacitinib would convey a benefit in cardiovascular (CV) risk reduction for PsA, noting that evidence suggests treatment with methotrexate either alone or in combination with a TNF-inhibitor in psoriasis is thought to convey a CV benefit for patients with existing CV risk (eg in patients with psoriasis who have inflammatory arthritis). Members also considered that, given the elevated CV risk in patients with severe and untreated arthritis, that reducing inflammation with any treatment might reduce CV risk.

9.21. The Committee noted the patient-reported outcomes (PRO) 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) (Strand et al. Rheumatol Ther. 2021;8:1827-44). The Committee considered that the benefits from upadacitinib according to the PRO measures appeared better than those reported as clinical scores.

9.22. The Committee noted that the supplier application also included evidence for upadacitinib from the phase III, randomised (1:1:1:1), double-blind SELECT-PsA 1 trial of upadacitinib 15mg daily vs upadacitinib 30mg daily vs adalimumab 40mg every other week vs placebo crossing over to upadacitinib 15mg at week 24 vs placebo crossing over to upadacitinib 30mg at week 24 in 1,705 patients with active PsA who had a history of inadequate response to at least one conventional synthetic DMARD (M15572 Week 24 Clinical Study Report [unpublished]). The Committee noted that the primary endpoint of SELECT-PsA 1 was ACR20 and was made aware of published 24-week data reporting non-inferiority of upadacitinib 15mg to adalimumab every other week and a similar higher incidence of infections with upadacitinib 15mg vs placebo or adalimumab (McInnes et al. N Engl J Med. 2021;384:1227-39). The Committee considered this evidence suggested that the ACR20 response with upadacitinib for PsA in the first-line was slightly better than the response in a second or subsequent line. The Committee considered this pattern was also seen in other diseases where there is third-line use of upadacitinib due to its mechanism of action, and considered that this decreasing benefit with each subsequent line was different to that seen with other bDMARDs for PsA.

9.23. The Committee noted the published results of the EXCEED trial, which reported secukinumab 300mg was non-inferior to adalimumab 40mg as first-line therapy in PsA (McInnes et al. Lancet. 2020;395:1496-1505); 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

9.24. The Committee noted that the evidence for secukinumab is mature at five years, has similar methodology and outcomes to the SELECT-PsA 1 trial, and reports an adverse event profile that is similar to that of other bDMARDs for PsA.

9.25. The Committee also noted the following evidence for upadacitinib or secukinumab in PsA:

- Nash et al. Rheumatology (Oxford). 2021;keab905. Online ahead of print
- Yates et al. Arthritis Rheumatol. 2021;73:779-88
- Burmester et al. Rheumatol Ther. 2022;9:521-39
- McInnes et al. RMD Open. 2022;8:e002049

9.26. Overall, the Committee considered that there was moderate evidence for benefits from upadacitinib for PsA from one randomised controlled trial, which provided short term data in a population comparable to the New Zealand population with PsA. The Committee considered that upadacitinib appears to benefit all patients with PsA and considered that it could also produce a benefit for family/whānau of people with PsA. The Committee noted that there was no direct comparative evidence of upadacitinib or secukinumab compared to a second anti-TNF after inadequate response from a first-line bDMARD, but considered that it was plausible there could be a benefit from a treatment with a different mechanism of action.

9.27. The Committee considered that good disease control was the main factor determining health system resource use regardless of the treatment type for PsA, and that patients with more controlled disease would likely have less requirement for outpatient visits (eg specialist consultation every two years). Members considered that better disease control may be associated with a reduction in joint surgery. Members also considered that the evidence linking biologic treatment to reduced surgery requirements is weak, and may be due to patients needing to present with severe disease and erosions at baseline to qualify for biologic treatment.

9.28. The Committee noted that oral upadacitinib would have a suitability benefit over subcutaneous secukinumab, which is generally self-administered by patients or is administered at home or in the community by health workers in a small number of cases. The Committee therefore considered there would be no substantial impact to healthcare workers if upadacitinib were funded for PsA. The Committee considered that the suitability of upadacitinib as an oral treatment would be of benefit especially to Māori and people who live in rural areas, who may find it more suitable and accessible than alternative treatments that are injected subcutaneously.

9.29. The Committee considered that there was unlikely to be a prevalent cohort of patients who would switch to upadacitinib second-line or third-line upon listing, although considered that Pharmac should seek the Rheumatology Advisory Committee's view on whether there is a prevalent group of patients who would switch to upadacitinib upon listing and what size that group might be.

9.30. The Committee considered that upadacitinib would most likely be used as a third-line treatment following secukinumab, especially for patients with pre-existing elevated CV risk who would benefit from other treatments first. However, the Committee considered that second-line use of upadacitinib would be expected if funding permitted this and considered that upadacitinib could gradually replace a portion of the current secukinumab second-line market (members noted the ACR and EULAR guidelines' authors considered upadacitinib may take part of the second-line market). The Committee considered that Pharmac should seek the Rheumatology Advisory Committee's view on the benefits and risks of second-line vs third-line use of upadacitinib for PsA, where upadacitinib would be used in the treatment paradigm, the current treatment sequencing for PsA, and whether upadacitinib would be used second-line for patients who received secukinumab first-line. The Committee considered that upadacitinib would not be used in combination with other treatments for PsA, as the risk of infection would be unacceptably high.

9.31. The Committee considered that secukinumab would be the appropriate comparator for upadacitinib second-line treatment, however, that it was unclear what was the appropriate comparator for upadacitinib in the third line, and considered that Pharmac should seek the

Rheumatology Advisory Committee's view, especially given potential variation in practice. The Committee considered that if upadacitinib was listed at the same line of treatment as secukinumab, this would still result in an extension in the length of time patients spend on treatment for PsA as patients would have access to a greater number of treatments. The Committee therefore considered that true cost-neutrality to the pharmaceutical budget may be difficult to achieve.

9.32. The Committee considered that Pharmac should seek the Rheumatology Advisory Committee's views of what elements should comprise Special Authority criteria for second-line and third-line use of upadacitinib for PsA.

9.33. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for upadacitinib if it were to be funded in New Zealand for second-line treatment of PsA. 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 Committee's assessment at this time and may differ from that requested by the applicant. The Committee noted that elements of the PICO for this application are unclear at this time. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Patients with psoriatic arthritis (PsA) who received inadequate benefit from **one prior biologic treatment** Assume that some patients would typically receive upadacitinib second-line (ie would receive upadacitinib as soon as it becomes available)
Intervention	Treatment sequencing in the intervention uncertain at this time, but the most common treatment sequence of is considered likely to be: First line anti-TNF (typically adalimumab) --> Second-line upadacitinib or secukinumab --> Third-line alternate agent of upadacitinib or secukinumab --> Last line second anti-TNF --> Supportive care
Comparator(s)	Treatment sequencing in the comparator unclear at this time, but the most likely comparator is secukinumab and the most common treatment sequence is considered likely to be: First line anti-TNF (typically adalimumab) --> Secukinumab second-line --> 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 Potentially lower health resource utilisation (eg inpatient, outpatient visits, surgery) vs supportive care due to lower disease activity Potentially lower cardiovascular risk vs supportive care due to lower disease activity
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.	

9.34. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for upadacitinib if it were to be funded in New Zealand for third-line treatment of PsA. 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 Committee's assessment at this time and may differ from that requested by the applicant. The Committee noted that elements of the PICO for this application are unclear at this time. The PICO may develop based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Patients with psoriatic arthritis (PsA) who received inadequate benefit from **two prior biologic treatments**
Intervention	Treatment sequencing in the intervention unclear at this time
Comparator(s)	Treatment sequencing in the comparator unclear at this time
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
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 ankylosing spondylitis (AS) following inadequate benefit from at least one biologic [P-001761] and for the treatment of AS following inadequate benefit from at least two biologics [P-001776]

Application

10.1. The Committee reviewed the application from AbbVie Limited for the use of upadacitinib (RINVOQ) for the second-line treatment for adult patients with active ankylosing spondylitis (AS) which has responded inadequately to conventional therapy with a biologic disease-modifying anti-rheumatic drug (bDMARD).

10.2. The Committee noted that Pharmac staff also sought the Committee's view of the potential benefits and risks of upadacitinib for the third-line treatment for adult patients with active AS which has responded inadequately to conventional therapy including two bDMARDs.

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

Recommendation

10.4. The Committee **recommended** upadacitinib be listed in the Pharmaceutical Schedule for the second-line treatment of AS only if **cost-neutral** to secukinumab.

10.4.1. In making this recommendation, the Committee considered that:

10.4.1.1. the data for upadacitinib was immature but suggests that upadacitinib is at least as effective as secukinumab in this setting

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

10.5. The Committee **recommended** upadacitinib be listed in the Pharmaceutical Schedule for the third-line treatment of AS with a **low priority**.

10.5.1. In making this recommendation, the Committee considered that:

10.5.1.1. the data for upadacitinib was immature but suggests that upadacitinib is at least as effective as secukinumab in this setting

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

10.5.1.3. patients with AS require subsequent treatments over their lifetime and that an additional option for third-line treatment would be beneficial for this population.

10.6. The Committee considered that Pharmac should seek further advice regarding upadacitinib for AS from the Rheumatology Advisory Committee, including the Committee's views of:

- The current sequencing of treatment with bDMARDs, including where secukinumab is currently used (ie after one prior anti-TNF or after two) and in what proportion(s) of patients
- The reason for lower uptake of secukinumab than anticipated for AS
- 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
- Whether there is a prevalent group of patients who would likely to switch to upadacitinib upon listing
- The number of people who might be started on upadacitinib, and the treatments that might be displaced
- Special Authority criteria for upadacitinib for second-line and third-line treatment of AS.

Discussion

Māori impact

10.7. The Committee considered that AS does not appear to disproportionately affect Māori, who experience lower prevalence of human leukocyte antigen B27 (HLA-B27) (present in more than 90% of all cases of AS) than non-Māori and noted that Māori account for 6.9% of all patients on bDMARD treatments for AS.

Discussion

10.8. The Committee noted that ankylosing spondylitis (AS) is an axial spondyloarthritis (axSpA), where axSpA is a complex family of chronic inflammatory diseases that encompasses both non-radiographic axSpA (nr-axSpA) and AS (also known as radiographic axSpA, with signs of sacroiliac joint involvement on x-ray); two diseases that are at either end of a spectrum. The Committee noted that AS ranges in severity and causes inflammatory back pain and progressive, irreversible spinal stiffness. The Committee noted that half of patients with AS have peripheral arthritis and extra-articular manifestations (eg enthesitis, fibromyalgia, depression, poor sleep) can also occur. The Committee noted that a diagnosis of AS is made according to a composite of clinical and radiographic features.

10.9. The Committee noted evidence from a systematic review and meta-analysis of studies in AS which reported a higher risk of death from all causes (pooled relative risk 1.64, 95% CI: 1.49-1.80, six studies) and from cardiovascular causes (RR 1.35, 95% CI: 1.01-1.81, three studies) in patients with AS compared with the general population (Chaudhary et al. Arthritis Care Res. 2021. Online ahead of print). The Committee considered that AS is probably associated with higher mortality that is mainly due to cardiovascular risk, although it was unclear whether the risk of mortality was greater in patients with more active disease compared with less active disease.

10.10. The Committee noted that AS onset occurs in a patient's 20s and 30s, that the disease affects more males than females, and that a family history of inflammatory bowel disease, psoriasis or uveitis confers a greater risk of developing AS. The Committee noted that

prevalence of AS depends on the definition used but is reported to be between 0.1% to 0.4%, equivalent to between 4,000 and 16,000 people in New Zealand; members considered it was difficult to be more precise perhaps because of different definitions of the disease. The Committee noted that about 1,500 people receive bDMARD treatment for AS with annual growth of 5%, and considered that a reasonable estimate would be that a quarter of all cases with AS diagnosed in New Zealand are treated with a bDMARD (although no local data was available to confirm this), meaning that 4,000 patients was the most likely estimate of the overall population with AS. Members were made aware of an unpublished Dunedin-based registry study and considered that this data may help to confirm the proportion of patients who are receiving bDMARDs for AS specifically, noting that some patients have AS but do not meet funding criteria due to lack of access to MRI and having disease that cannot be seen on plain x-ray. Members considered the existing and proposed Special Authority criteria require baseline disease severity that is high, and considered that patients with severe unilateral sacroiliitis may be ineligible for funded treatment and thus not contribute to the number of patients with AS on bDMARDs.

10.11. The Committee noted 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 considered that AS does not appear to disproportionately affect Māori, who experience lower prevalence of HLA-B27. The Committee noted that Māori account for 6.9% of all patients on bDMARD treatments for AS, but considered that this figure may underrepresent the true number of Māori with AS of this severity due to barriers and disparities affecting diagnosis and access to care.

10.12. The Committee noted that several measures are used to assess disease activity and functional impairment in clinical practice and/or in clinical trials for AS:

10.12.1. 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. Members considered that the BASDAI is an imperfect tool but remains the best available.

10.12.2. 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. Members considered that the BASFI can give a good indication of disease activity and function.

10.12.3. The Assessment in Ankylosing Spondylitis (ASAS) response criteria which requires 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). The Committee noted that the ASAS was a clinical trial measure not used in clinical practice.

10.13. The Committee noted that the aims of treatment of AS are to alleviate symptoms, improve functioning, maintain the ability to work, decrease disease complications and delay skeletal damage as much as possible. The Committee considered that first-line bDMARD treatment for AS would be with adalimumab for most patients (otherwise etanercept), then second-line treatment would be with secukinumab given as a four-weekly subcutaneous injection, which has been funded since May 2021. The Committee noted that clinical trials require a BASDAI of 4 for entry, considered that the current Special Authority requirement (for a BASDAI score of 6 and radiographic evidence of irreversible structural changes) for access to funded anti-tumour necrosis factor (anti-TNF) treatment with adalimumab or etanercept to be a high threshold, and noted that a 50% improvement from initial BASDAI score is needed to continue funded treatment (BASDAI50). The Committee considered it was unclear whether secukinumab was used second-line after one prior bDMARD and/or third-line after both adalimumab and etanercept, but considered it likely that secukinumab would become the preferred second-line option over time. Members thought it not unreasonable to estimate perhaps roughly two-thirds of patients who receive inadequate benefit from a

first-line anti-TNF would be likely to receive treatment with secukinumab, although considered this would be gradual over years. The Committee considered there was uncertainty in the current treatment paradigm (including where secukinumab is currently used and in what proportion(s) of patients, and the reason for lower uptake of secukinumab than anticipated for AS), and that Pharmac should seek advice from Rheumatology Advisory Committee regarding this.

10.14. The Committee considered that most patients cycle through all available bDMARDS treatments, possibly including some treatment-free intervals, as their disease eventually becomes active again or they lose response to treatment. The Committee considered it likely that some patients remain on treatment despite not experiencing the BASDAI50 response required to meet renewal criteria for AS, and considered that patients who received about a 30% response would be assessed as receiving a clinically useful benefit. The Committee considered that patients who receive smaller benefits from treatment (eg. a 20% improvement in BASDAI or ASAS score) would be unlikely to stay on treatment, particularly if other funded options were available.

10.15. The Committee was made aware of evidence that loss of benefit with current treatment is associated with decreased work productivity, increased absenteeism and presenteeism, and greater impairment in daily activities in AS (Deodhar et al. BMC Rheumatol. 2020;4:19), and evidence that the proportion of patients remaining on treatment for AS decreases with each course (Glintborg et al. Arthritis Rheum. 2013;65:1213-23). The Committee considered that, while each sequential line of treatment provides a decreasing magnitude of benefit, patients may remain on their first anti-TNF therapy for a very long time, as there are few other funded options. The Committee considered that real-world persistence on secukinumab would be higher than that reported in clinical trials, and was made aware of an abstract reporting overall adherence to secukinumab of 64.5% at one year in 311 patients with AS (Klitz et al. Ann Rheum Dis. 2019; 78(Suppl 2):1814.2-15).

10.16. Members considered that patients with AS experience a significantly lower quality of life compared with the general population and have physical health that is comparable to that of people with rheumatoid arthritis. The Committee was made aware of evidence from a cross-sectional study of the costs associated with AS/axSpA at two hospitals in New Zealand which reported that, of 81 patients with AS, about half used bDMARDs, 42% had some mobility problems, 20% had some problems with self-care, over half had some problem with usual activities, 80% had moderate pain or discomfort, and about a third had moderate anxiety or depression (White et al. N Z Med J. 2019;132:38-47). The Committee considered that there was evidence of a broad reduction in quality of life in the study population of patients attending specialist clinics, although noted that patients with well-controlled disease or those not on bDMARDs may not be seen much in specialist clinics.

10.17. The Committee considered that the families and whānau of people with AS also had an unmet health need with the loss of employment and family impact associated with AS. The Committee considered that people with AS have an unmet health need despite the currently available treatments, given the lifelong nature of the disease requiring subsequent treatments over the patient's lifetime. The Committee considered that an additional treatment option would be beneficial especially in the third line.

10.18. The Committee noted that upadacitinib is an oral, selective Janus Kinase-1 (JAK1) inhibitor (JAKi) and is a targeted synthetic treatment. Members considered that there does not appear to be an overall JAKi class effect yet identified, but considered that subclasses of JAKi exist and that these types have similar effects and subtle differences depending on the indication. The Committee noted that upadacitinib is Medsafe-approved for the treatment of active AS, in effect, in adult patients for whom one or more conventional therapies have not provided an adequate response or are not tolerated. The Committee noted that the proposed dosing for upadacitinib in AS is 15mg daily.

10.19. The Committee noted that the application proposed upadacitinib be funded as a second or subsequent treatment for AS following the use of one or more of the biologic disease-

modifying anti-rheumatic drugs (bDMARDS) adalimumab and/or etanercept, and that the comparator proposed was secukinumab.

10.20. The Committee noted that the key evidence for upadacitinib in AS comes from SELECT-AXIS 2, a phase III, multicentre, randomised (1:1), double-blind, placebo-controlled study that included 420 adult patients with active AS who had BASDAI score of four or greater and who received an inadequate response from or experienced an intolerance to one or more bDMARDs (bDMARD-IR AS). The Committee noted that the study contained two parts, however, the submission provided data confined to unpublished results from the Clinical Study Report (CSR) of Study 1 (ie the first part of SELECT-AXIS 2 overall), which included the 420 patients with active AS. The Committee noted the Study 1 CSR had been provided by the applicant in confidence [note the applicant has made available the following information from the Study 1 CSR for this meeting record]:

10.20.1. The Committee noted that SELECT-AXIS 2 Study 1 participants received either oral upadacitinib 15 mg once daily or matched oral placebo followed by upadacitinib 15 mg once daily, as placebo group subjects were switched to upadacitinib 15 mg once daily at Week 14.

10.20.2. The Committee noted that the primary endpoint of SELECT-AXIS 2 Study 1 in the bDMARD-IR AS population was ASAS40 response rate at Week 14, which was achieved by 94/211 (44.5%) of patients who received upadacitinib vs 38/209 (18.2%) of patients who received placebo [M19-944 Clinical Study Report – Week 14 Study 1 (bDMARD-IR AS) (Unpublished)].

10.20.3. The Committee noted that the BASDAI50 response rate at week 14 in SELECT-AXIS 2 Study 1 was 43.1% with upadacitinib vs 16.7% with placebo.

10.20.4. The Committee noted that a 90-week open label extension of SELECT-AXIS 2 in which both treatment groups received upadacitinib 15 mg was planned but that efficacy data to 104 weeks was not available and completion was anticipated in 2025. The Committee noted that the evidence for upadacitinib in AS was not as well advanced as the evidence for upadacitinib in psoriatic arthritis (PsA), where clinical trial data was available to 56 weeks.

10.20.5. The Committee noted an improvement in quality of life with upadacitinib vs placebo in SELECT-AXIS 2 Study 1 at week 14, with between-group differences in AS quality of life (ASQoL) and Assessment of SpondyloArthritis international Society Health Index (ASAS HI) of -3.07 and -1.85, respectively (each $P< 0.0001$). The Committee considered that the study reported a significant effect on global pain, back pain, quality of life and work impairment with values all greater than the minimal clinically important difference (MCID). Members considered that it was feasible that these results could be further improved after one year.

10.20.6. The Committee noted that safety data from SELECT-AXIS 2 Study 1 was reported up to 33 weeks, and that treatment-emergent adverse events (AEs) were reported in 40.8% of upadacitinib patients vs 36.8% of placebo patients.

10.21. 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 Committee noted that SELECT-AXIS 1 reported improvement in ASAS40 and BASDAI50 at one year in bDMARD naïve patients, and considered that, from 16 weeks to 64 weeks, the improvement gradually continued. The Committee considered this was encouraging, given the limited 16-week data for the target population in the second line.

10.22. The Committee was made aware of pooled safety data from the SELECT-PsA 1 and SELECT-PsA 2 trials in which 2,257 patients with psoriatic arthritis received at least one dose of upadacitinib 15 mg (N = 907) or 30 mg (N = 921) for 2504.6 patient years (PY) of

exposure, or adalimumab 40 mg every other week for 549.7 PY of exposure (Burmester et al. Rheumatol Ther. 2022;9:521-39). The Committee was also made aware of safety data from a pooled analysis of patients who received upadacitinib 15mg for rheumatoid arthritis (7,023 PY), psoriatic arthritis (1247 PY) and AS (291 PY) compared with adalimumab (RA and PsA) or methotrexate (RA) (Burmeister et al. Arthritis Rheumatol. 2021;73 (suppl 10):Abstract Nr. 1691; Shaw et al. Rheumatol. 2022;61(suppl_1):Abstract Nr. P220). The Committee noted that the only statistically significant difference with upadacitinib compared with adalimumab or placebo were an increase in opportunistic infections (primarily pneumonia) and herpes zoster, which are known associations. The Committee considered that this data was reassuring in the context of using upadacitinib specifically in AS, and did not include a signal for thromboembolic events reported to be associated with another JAK inhibitor, tofacitinib (JAK 1 and 3).

10.23. The Committee noted that the supplier had reviewed evidence for secukinumab in AS from MEASURE 2, a phase III, multicentre, randomised (1:1:1), double-blind, placebo-controlled three-arm study of 219 patients with AS fulfilling the modified New York criteria, with BASDAI score of four or greater despite treatment with the maximum doses of non-steroidal anti-inflammatories (NSAIDs) (Baeten et al. N Engl J Med. 2015;373:2534-48; Sieper et al. Ann Rheum Dis. 2017;76:571-92). The Committee noted that participants received either secukinumab 150 mg, secukinumab 75 mg, or placebo for 16 weeks, then placebo patients were randomly reassigned to one of the secukinumab doses for the rest of the five-year study. The Committee noted that 38.8% (N=85/219) of patients were antiTNF-experienced and had received only one prior bDMARD.

10.23.1. The Committee noted that the primary endpoint of MEASURE 2 was the ASAS20 response rate at week 16, which was 61% with secukinumab 150 mg vs 41% with secukinumab 75 mg vs 28% with placebo (P<0.001 and P=0.10 for comparisons of the higher and lower doses, respectively, with placebo). The Committee noted that the ASAS40 response rate at week 16, a secondary endpoint, was 36% with secukinumab 150 mg vs 26% with secukinumab 75 mg vs 11% with placebo (P<0.001 and P=0.10 for comparisons of the higher and lower doses, respectively, with placebo). The Committee noted the supplier application reported the ASAS20 response in the MEASURE 2 IR subset (N=14/28), with odds ratio of 3.14 (95% CI: 1.02 to 9.71) and relative risk of 2.07 (95% CI: 1.22 to 3.51).

10.23.2. The Committee noted further evidence from MEASURE 2 reported at two, three, and five years (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). The Committee noted that ASAS 20 and 40 response rates with secukinumab 150 mg at week 156 were 70.1% and 60.9%, respectively, compared with results at week 52 which were 74.2% and 57.0%, respectively; however, there was a slight decrease for secukinumab 75mg (54.3% and 37.0% vs 62.5% and 43.2%, respectively).

10.24. The Committee noted evidence from MEASURE 4, a multicentre, randomised (1:1:1), double-blind, placebo-controlled study of 350 patients with AS fulfilling the modified New York criteria, with BASDAI score of four or greater despite treatment with the maximum doses of NSAIDs (Kivitz et al. Rheumatol Ther. 2018;5:447-62). The Committee noted that participants received either secukinumab 150 mg with a loading dose, secukinumab 150 mg without a loading dose, or placebo for 104 weeks. The Committee noted that 27.7% (N=97/350) of patients were antiTNF-experienced and had received only one prior bDMARD. The Committee noted that the primary endpoint of MEASURE 4 was ASAS20 at week 16, which was 59.5% and 61.5%, respectively, for the 150 loading and no loading groups vs placebo (47%; P=0.057 and P=0.054, respectively), and that the primary endpoint was not met. The Committee noted the supplier application reported that the ASAS40 response was not statistically significant in MEASURE 4 in the bDMARD-IR subset (N=11/31), with OR of 1.79 (95% CI: 0.61 to 5.27) and RR of 1.51 (95% CI: 0.87 to 2.62) at 16 weeks, nor was the RR significant for ASAS20 in IR subset (N=18/31) (RR 1.41; 95% CI: 0.84 to 2.38).

10.25. The Committee considered that the characteristics of patients in the MEASURE trials were generally similar to those in the SELECT-AXIS trials, predominantly including males with a diagnosis of AS for five to eight years. The Committee noted that SELECT AXIS 2 included patients who had received one or two previous bDMARDS, however, MEASURE 2 and 4 each included patients who had received only one previous bDMARD. The Committee noted that patients in Select-AXIS 2 had higher median high-sensitivity C-reactive protein (hsCRP) levels than MEASURE 2 and 4 patients, and greater total back pain and patient global assessments were reported in SELECT-AXIS 2 patients.

10.26. Overall, the Committee considered that the data for upadacitinib was immature but that at 14 weeks, the ASAS40 and BASDAI50 responses were significant and suggest that upadacitinib could be at least as effective as secukinumab in patients experiencing an inadequate response to prior bDMARDs. The Committee considered that the evidence for upadacitinib in AS to be of low strength, being from a single large but short-duration study for which 52-week data is not yet available and which has not been peer reviewed or published, although members considered that the quality and design of the study to be good. Members considered that there appeared to be no difference in risk or benefits of upadacitinib for second- vs third-line use, based on the trial data reviewed. The Committee considered that the available evidence for the safety of treatments for AS indicates an acceptable safety profile with upadacitinib relative to other treatments. The Committee considered that upadacitinib would benefit a broad group of patients with AS and would be expected to provide a benefit to their family/whānau.

10.27. The Committee considered that secukinumab was a reasonable comparator for upadacitinib in the second line and that upadacitinib would likely be used after one prior bDMARD if permitted by funding criteria. However, the Committee considered that it was unclear what was the appropriate comparator for upadacitinib in the third line setting for AS and what subsequent treatments might be, and considered that Pharmac should seek the Rheumatology Advisory Committee's view on this, especially given potential variation in practice. Members thought that if upadacitinib were funded, secukinumab usage may likely decrease and thought it not unreasonable to assume that uptake of upadacitinib could be faster than the uptake for secukinumab. The Committee considered that if upadacitinib was listed at the same line of treatment as secukinumab, this would still result in an extension in the length of time patients spend on treatment for AS, as patients would have access to a greater number of treatments sequentially. The Committee therefore considered that true cost-neutrality to the pharmaceutical budget may be difficult to achieve.

10.28. The Committee considered that, if funded for AS, it was unclear how many people might be started on upadacitinib and whether there was a prevalent group of patients who would likely to switch to upadacitinib upon listing, and considered that Pharmac should seek the Rheumatology Advisory Committee's view of this.

10.29. The Committee considered that Pharmac should also seek the Rheumatology Advisory Committee's views of what elements should comprise Special Authority criteria for second-line and third-line use of upadacitinib for AS.

10.30. Members considered that the evidence reviewed did not suggest whether patients who gain a response to treatment require fewer hospitalisations, outpatient visits or ED visits, nor did it suggest whether effective treatment was associated with a reduction in mortality for patients with AS.

10.31. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for upadacitinib if it were to be funded in New Zealand for second-line treatment of AS. 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 Committee's assessment at this time and may differ from that requested by the applicant. The Committee noted that elements of the PICO for this application are unclear at this time. The

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

Population	Patients with ankylosing spondylitis (AS) who received inadequate benefit from **one prior bDMARD treatment** Assume that patients would typically receive upadacitinib second-line (ie would receive upadacitinib as soon as it becomes available)
Intervention	Treatment sequencing in the intervention uncertain at this time, but the most common treatment sequence is likely to be: First line anti-TNF (typically adalimumab) --> Second-line upadacitinib or secukinumab --> Third-line alternate agent of upadacitinib or secukinumab --> Last line second anti-TNF --> Supportive care
Comparator(s)	Treatment sequencing in the comparator uncertain at this time, but the most common treatment sequence is likely to be: First line anti-TNF (typically adalimumab) --> Secukinumab second-line --> Second anti-TNF --> supportive care
Outcome(s)	Improved rates of clinical response (as measured by ASAS20/40, BASDAI 50) vs supportive care Improved quality of life from fewer signs and symptoms of ankylosing spondylitis vs supportive care Based on indirect comparisons, extrapolated to assume similar benefit of upadacitinib to secukinumab Assumes no reduction in mortality with successful treatment, given uncertain relationship between disease severity and mortality
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.	

10.32. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for upadacitinib if it were to be funded in New Zealand for third-line treatment of AS. 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 Committee's assessment at this time and may differ from that requested by the applicant. The Committee noted that elements of the PICO for this application are unclear at this time. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Patients with ankylosing spondylitis (AS) who received inadequate benefit from **two prior bDMARD treatments**
Intervention	Treatment sequencing in the intervention unclear at this time
Comparator(s)	Treatment sequencing in the comparator unclear at this time
Outcome(s)	Improved rates of clinical response (as measured by ASAS20/40, BASDAI 50) vs supportive care Improved quality of life from fewer signs and symptoms of ankylosing spondylitis vs supportive care Based on indirect comparisons, extrapolated to assume similar benefit of upadacitinib to secukinumab Assumes no reduction in mortality with successful treatment, given uncertain relationship between disease severity and mortality
"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.	

11. Bevacizumab for the treatment of advanced ovarian cancer

Application

11.1. The Committee reviewed the application for bevacizumab for the treatment of advanced ovarian cancer.

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

Recommendation

11.3. The Committee **recommended** that bevacizumab for the first-line treatment of high-risk advanced ovarian cancer be listed with a **medium** priority, subject to the following special authority criteria:

> **BEVACIZUMAB**
> **Initial application - Advanced or metastatic ovarian cancer**
> Applications only from a relevant specialist or relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:
> Either
> 1. The patient has previously untreated advanced (FIGO Stage IIIB or IIIC) sub-optimally debulked (maximum diameter of any gross residual disease > 1cm) epithelial ovarian, fallopian tube, or primary peritoneal cancer; or
> 2. The patient has FIGO Stage IV epithelial ovarian, fallopian tube, or primary peritoneal cancer; and
> 3. All of the following
> 3.1. Maximum cumulative dose of 135 mg/kg (12 months' treatment), and
> 3.2. 18 weeks concurrent treatment with chemotherapy is planned, and
> 3.3. Bevacizumab is to be discontinued at disease progression.

11.4. In making this recommendation, the Committee considered:

- The high unmet need in patients with advanced ovarian cancer, in particular those with a BRCA-negative diagnosis.
- The low- to moderate-strength, high-quality evidence that first-line treatment with bevacizumab improves progression-free survival (PFS) and overall survival (OS) in those with advanced, high-risk ovarian cancer.
- The limited funded alternatives for people with advanced ovarian cancer

- Increased prevalence among Māori and Pacific peoples

11.5. The Committee **recommended** that bevacizumab for the second-line treatment of high-risk advanced ovarian cancer be **declined**. In making this recommendation, the Committee considered that second-line treatment with bevacizumab provides a small beneficial effect on PFS and little to no improvement in OS in those with advanced, high-risk ovarian cancer.

Discussion

Māori impact

11.6. The Committee noted that ovarian cancer has roughly proportionate incidence in Māori (n=31, approximately 15% of new cases) compared with non-Māori (n=229, approximately 85%) in New Zealand (Ministry of Health [MoH].. 2019). The Committee noted that it has been reported that Māori have a higher mortality rate compared with non-Māori, non-Pacific peoples (Firestone et al. J Epidemiol Community Health. 2009;63:814-9). It was also noted that Lakes District Health Board (LDHB) reported that ovarian cancer was 2.8 times as common for Māori while the mortality rate was 5.7 times as high as non-Māori (LDHB Māori Health Profile 2015). The Committee considered that Māori present with ovarian cancer at an earlier age in life compared to non-Māori (Robson et al. Unequal Impact: Māori and Non-Māori Cancer Statistics 1996-2001. Wellington: Ministry of Health, 2005). The Committee considered that the overall data in this area is uncertain, given the diverse estimate of both comparative incidence of, and mortality rates from, ovarian cancer in Māori and non-Māori.

11.7. The Committee considered that improved treatment options for patients with ovarian cancer may provide health equity benefits, noting the high incidence of ovarian cancer and mortality for Māori compared with other populations. The Committee noted that the treatment of cancer is a specific health priority for the Government and under Pharmac's Hauora Arotahi (Māori health areas of focus).

Background

11.8. The Committee noted that this funding application has been previously reviewed by PTAC in 2014 and by the Cancer Treatments Subcommittee (CaTSoP) in 2015, with each recommending decline. The Committee noted that these recommendations were based on the results available at the time for four randomised trials (ICON7, GOG-0218, OCEANS, and AURELIA; two being blinded, two open-labelled) that reported some OS benefit only for high-risk patients who were treated with bevacizumab and combined chemotherapy in the-first line of therapy. In addition, it was noted that at that time the drug was expensive, and its use was associated with a lower health-related quality of life (HRQoL) compared to patients having combined chemotherapy alone. The Committee noted that the funding application for bevacizumab for advanced ovarian cancer was proposed for progression to decline following CaTSoP's recommended to decline in September 2015.

11.9. The Committee noted that Pharmac had received consultation feedback from two patient support groups (Cure Our Ovarian Cancer and Talk Peach Gynaecological Foundation) indicating there is updated clinical trial evidence and noting that the price of bevacizumab since first consideration had reduced with the introduction of biosimilars. The Committee noted that this submission also included reflections from whānau of those with ovarian cancer, highlighting the unmet health need. The Committee agreed with Pharmac staff that the availability of this additional information warranted further assessment of the use of bevacizumab in advanced ovarian cancer.

Discussion

11.10. The Committee noted that ovarian, fallopian tube, and peritoneal carcinomas are closely related in that they have similar histology and patterns of clinical behaviour. The Committee noted that these cancers follow relapsing and remitting disease courses, in which patients receive sequential rounds of therapy and experience progressively shorter intervals between treatments and relapses.

11.11. The Committee noted that ovarian cancer alone was among the ten most commonly registered cancers in women in New Zealand in 2019, with an incidence of diagnosis of 7.1 per registrations per 100,000 female population per year (MoH. New Cancer Registrations 2019). The Committee noted that in 2013, the mortality rate from ovarian cancer in New Zealand was 4.6 deaths per 100,000 in the female population; the lowest mortality rate for ovarian cancer over the previous decade (MoH. Cancer Trends 2013). It was noted that the survival rates for patients with ovarian cancer were noted by PTAC in May 2017 to be 65%, 36% and 31% at 1, 5, and 10 years respectively. The Committee noted that health outcomes observed in Māori are also reflected in Pacific peoples, with an age-standardised rate of ovarian cancer of 25.4 per 100,000 (95% confidence [CI] 20.2 to 30.2) compared to 18.7 per 100,000 (95% CI 18.1 to 19.4) for European/other women (Meredith et al. Cancer Causes Control. 2012;23:1173-84).

11.12. The Committee noted that patients with ovarian cancer may have reduced HRQoL from early in their treatment course due to surgery causing premature menopause and sexual dysfunction. The Committee noted that chemotherapy for ovarian cancer is known to be associated with significant toxicities, such as nausea, neutropenia, alopecia, anaemia, and fatigue, some of which can remain long-term (eg peripheral neuropathy). The Committee noted that with more advanced disease, patients may develop pleural effusions, abdominal masses which can lead to bowel obstruction, or ascites which may require repeated drainage. The Committee considered the average life expectancy of patients with advanced disease to be three years and noted that about 70% of patients with ovarian cancer will experience relapse within two years following standard first-line treatment. The Committee noted that subsequent lines of therapy may utilise treatments that have been used previously (eg additional chemotherapy) and are often given with palliative intent. The Committee also considered that QoL is disproportionately worse for family and caregivers of patients with ovarian cancer (Le et al. Obstet Gynecol Surv. 2003;58:749-58).

11.13. The Committee noted that first-line treatment of patients with newly diagnosed advanced ovarian cancer consists of debulking surgery with or without radiotherapy followed by platinum-based chemotherapy (carboplatin or cisplatin, with paclitaxel). The Committee noted that patients who receive partial or complete response to chemotherapy and have documentation confirming pathogenic germline BRCA1/2 gene mutation are then eligible (from 1 August 2022) to receive olaparib treatment (as a maintenance treatment ongoing for partial responders, and for two years maximum for complete response). The Committee considered that treatment options for non-BRCA1/2 patients are limited.

11.14. The Committee noted that bevacizumab is a recombinant humanised monoclonal antibody that selectively binds to and neutralises the biologic activity of human vascular endothelial growth factor, thereby reducing tumour angiogenesis and inhibiting tumour growth (Medsafe Datasheet: Avastin (bevacizumab). 2021). The Committee noted that bevacizumab is Medsafe approved for the treatment of epithelial ovarian, fallopian tube or primary peritoneal cancer. The Committee noted that the recommended dose of bevacizumab in first-line treatment is 15 mg/kg once every three weeks via intravenous infusion when administered in combination with carboplatin and paclitaxel for up to six cycles of treatment, followed by continued use of bevacizumab as single agent, continued for a total of 15 months therapy or until disease progression (whichever occurs earlier).

11.15. The Committee briefly reprised the evidence previously considered (the ICON7, GOG-0218, OCEANS, and AURELIA trials) current at that time, and noted the additional following key updated evidence for bevacizumab in the treatment of advanced ovarian cancer:

11.15.1. The Committee noted again that ICON7 had been a phase III, randomised, open-label, international trial that compared the efficacy of carboplatin and paclitaxel with or without bevacizumab (7.5 mg/kg every 3 weeks) in 1528 patients with newly diagnosed ovarian cancer that was either high-risk early-stage (FIGO stage I-IIA, grade 3, or clear-cell histology) or advanced (FIGO stage IIB-IV). The Committee considered updated evidence from ICON7 in the form of retrospective exploratory post-hoc subgroup analyses by disease stage and extent of residual disease after upfront surgery (Martin et al. Gynecol Oncol. 2019;152:53-60). The Committee noted that after a treatment duration of 12 months, the PFS benefit from bevacizumab was reported to be consistent across all subgroups examined. The Committee noted that the PFS hazard ratio (HR) was 0.77 (95% CI 0.59 to 0.99) in 411 patients with stage IIIB-IV ovarian cancer with no visible residuum and 0.81 (95% CI, 0.69 to 0.95) in 749 patients with stage IIIB-IV disease and visible residuum. The Committee noted that no OS difference was detected in any subgroup except the previously described high-risk subgroup. The Committee noted that safety results in analysed subgroups were consistent with the overall study population. The Committee reiterated the methodological limitations and lessened evidence quality of post-hoc subgroup analyses, and the need for caution interpreting them.

11.15.2. The Committee noted that AURELIA had been a phase III, open-label, randomised trial that compared the efficacy of chemotherapy with or without bevacizumab (15 mg/kg IV for 21-day cycles) in 361 patients with platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer. The Committee noted updated evidence from AURELIA in the form of further analysis of this trial (sponsored by Roche) examining the chemotherapy arm (n=182) and compared patients that crossed over to bevacizumab (40%) with those who did not (60%) (Bamias et al. Ann Oncol. 2017;28:1842-8). The Committee noted that the crossover group experienced superior survival but considered that these results were not equivalent to that of a randomised trial given that crossover allocation is selective. The Committee reiterated the methodological limitations, interpretative challenges, and lessened evidence quality with cross-over analyses in this trial, requiring caution in interpretation. The Committee considered that, given the side effect profile of bevacizumab, it would be highly likely that those deemed unsuitable for crossover had clinical characteristics placing them at higher risks of disease progression and death.

11.15.3. The Committee noted new trial evidence in the form of JGOG3023, a phase II, randomised, open label, multicentre trial that compared the efficacy of chemotherapy with or without bevacizumab (dose published as “15 mg/m^2“ IV for 21-day cycles) in 106 patients with platinum-resistant ovarian cancer whose disease had progressed after bevacizumab plus chemotherapy. The Committee noted that after 6 months PFS was 3.1 months in the chemotherapy group and 4.0 months in the chemotherapy + bevacizumab group (HR=0.54, 95% CI: 0.32 to 0.90, *P*=0.0082), and that the median OS was 11.3 and 15.3 month in each group, respectively (HR=0.67, 95% CI 0.38 to 1.17, *P*=0.1556). The Committee noted that the incidence of grade ≥3 treatment-related adverse events (AEs) was 42.0% and 54.9%, with only 2 and 12 events leading to discontinuation of therapy, respectively (Shoji et al. Cancer Sci. 2022;113:240-50). The Committee noted the stated dose of bevacizumab as published, “15 mg/m^2”, was clearly incorrect (the correct dose would have been 15 mg/kg) and considered this could raise questions about the overall quality of the trial, alongside the known limitations of non-blinding in trials.

11.15.4. The Committee was made aware of GOG-0213; a phase III, multicentre, open-label, randomised trial that examined the efficacy of chemotherapy with and without bevacizumab (15 mg/kg IV for 21-day cycles) in women with ovarian cancer recurring 6 months after completion of initial therapy. The Committee noted that after a median follow up of 49.6 months, median OS in the chemotherapy plus bevacizumab group was 42.2 months (95% CI 37.7 to 46.2) vs. 37.3 months (95% CI 32.6 to 39.7) in the chemotherapy group (HR=0.829; 95% CI 0.683 to 1.005; *P*=0.056). It was also noted that there was no difference in HRQoL scores. The Committee noted that 96% of those in the chemotherapy plus bevacizumab group had at least one grade 3 or worse AE compared with 86% in the chemotherapy group, with the most frequently reported AEs being

hypertension (12% vs. 1%, respectively), fatigue (8% vs. 2%), and proteinuria (8% vs. none) (Coleman et al. Lancet Oncol. 2017;18:779-1).

11.15.5. The Committee was made aware of several single arm studies (OSCAR, ROSiA, REBECA), which were considered to indicate that, in many jurisdictions, bevacizumab has become part of the first-line standard of care for patients with advanced ovarian cancer, especially those at high risk (Hall et al. Int J Gynecol Cancer. 2020;30:213-20; Korach et al. J Surg Oncol. 2019;120:786-93; Lavacchi et al. Transl Cancer Res. 2020;9:402-4). The Committee considered that the PFS observed in these studies was similar to that seen in the ICON7 and GOG-0218 trials. The Committee considered that the assumption of bevacizumab being a part of first-line care is so strong that in newer comparative trials it is regarded as standard therapy.

11.15.6. The Committee was also made aware of a meta-analysis comparing bevacizumab to polymerase inhibitors (PARPi) in women with newly diagnosed ovarian cancer. The Committee noted that the PARPi are indicated in those with ovarian cancer with a BRCA1/2 mutation. The Committee noted that the study concluded that PARPi may be a more effective therapeutic strategy than bevacizumab with respect to PFS, and that the risk of serious AEs posed by PARPi and bevacizumab are similar in women with newly diagnosed BRCA1/2 ovarian cancer (Suh et al. BMC Cancer. 2022;22:346).

11.16. The Committee considered that the evidence provided was of low- to moderate-strength and high quality, and that it demonstrated the health benefit of bevacizumab in the treatment of advanced ovarian cancer. The Committee considered this benefit to be greatest in high-risk patients in first-line setting, with a smaller, less certain benefit in second-line treatment of patients with relapsed disease.

11.17. The Committee considered that first-line treatment with bevacizumab in doses of either 7.5 mg/kg or 15 mg/kg every three weeks improves PFS in patients with advanced ovarian cancer compared with placebo. The Committee considered that the value of PFS is offset by detriments in HRQoL related to the AE profile of the drug. The Committee considered that bevacizumab as first line treatment improves OS in those with Stage IV disease and, possibly, those with inoperable or sub-optimally debulked Stage III disease compared with placebo. The Committee considered that, when used as second-line therapy, bevacizumab has a small beneficial effect on PFS, and that one trial (AURELIA) reported a measurable HRQoL improvement with bevacizumab, whilst noting there may be methodological problems with that analysis related to the treatment of missing data. The Committee considered that the OS is likely not altered in the second-line setting, however one study in platinum-sensitive patients (GOG213) reported a borderline improvement. The Committee was made aware that there has been a shift in opinion amongst the oncology research community around the validity of PFS when matched against OS as gold standard, and that PFS is now accepted as an appropriate endpoint in some cancers, this including gynaecological cancers.

11.18. The Committee considered that the pivotal trials suffered from methodological issues: ICON7 was an open-label study and one of its published reports (Oza et al. Lancet Oncol. 2015;16:928-39) contained a typographical error that understated the overall mortality in the group of high-risk patients using bevacizumab (“54%” when it should have been 64%, from 158 deaths of 248 patients in that group; in the context of 69% deaths in the high-risk patients using chemotherapy group); GOG-0218 (Burger et al. N Engl J Med. 2011;365:2473-83; Tewari et al. J Clin Oncol. 2019;37:2317-28) was a double-blinded RCT, however the only group that had benefitted (Stage IV patients treated with both concomitant and maintenance bevacizumab) was reasonably small (n=92 by three years, n=53 by 5 years, HR 95% CI 0.59 to 0.95), with the possibility of Type I statistical error in addition to the inherent problems associated with being a post-hoc analysis.

11.19. The Committee noted that the ICON7 study protocol used a dose of 7.5mg/kg of body weight every 3 weeks, which differs from the recommended dose stated in the Avastin Medsafe datasheet and the doses used in other trials. The Committee noted that the

original application acknowledged this difference and suggested that this did not modify (with any statistical significance) any treatment benefit for PFS or OS. The Committee considered it reasonable to assume that most patients would utilise dosing of 7.5 mg/kg.

11.20. The Committee considered that, if funded access were to be widened, use of infusion services may remain unchanged for the initial cycles as bevacizumab would be administered in combination with other chemotherapy infusions. However, due to the option of further cycles of bevacizumab treatment continuing after that initial phase, it was noted that continued use this may add to the infusion service burden of work at hospitals and cancer day-stay facilities.

11.21. The Committee noted that there is also a risk of bevacizumab-related AEs (eg hypertension, proteinuria, muco-cutaneous bleeding, bowel perforations), which could potentially increase the burden on the health system. The Committee considered that those receiving bevacizumab treatment may also require monthly safety monitoring with a medical oncologist but there was unlikely to be any additional requirement for laboratory monitoring compared to currently funded chemotherapies.

11.22. The Committee considered, following clinician correspondence, that approximately 5% of high-risk ovarian cancer patients would not receive bevacizumab due to bowel obstruction, 10% would not receive it on the grounds of poor functional status or would personally decline the drug, and a further 15% would likely have germline BRCA1/2 mutations (and would be better candidates for treatment with olaparib). It was therefore considered that approximately 70% of eligible patients would be treated with bevacizumab if funded access were to be widened. The Committee considered that bevacizumab would not be used as a replacement for another treatment, but rather it would be given in addition to current regimens.

11.23. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for bevacizumab if it were to be funded in New Zealand for first-line advanced ovarian cancer. 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 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	Patients with high risk (stage IV or inoperable/sub-optimally debulked stage III) ovarian cancer, first line
Intervention	Bevacizumab, in combination with paclitaxel and carboplatin • Bevacizumab at 7.5 mg/kg, paclitaxel at 175 mg/m^2 and carboplatin at 5 AUC/mL on day 1, every three weeks for six cycles. • Followed by up to 12 three-weekly cycles of bevacizumab 7.5 mg/kg for a maximum total bevacizumab dosage of 135 mg/kg (18 cycles) or until disease progression or unacceptable toxicity, whichever occurs first.
Comparator(s) (NZ context)	Paclitaxel and carboplatin. • Three-weekly paclitaxel at 175 mg/m^2 and carboplatin at 5 AUC/mL on day 1, continuous until disease progression or unacceptable toxicity; usually six cycles (eviQ).
Outcome(s)	Increased PFS • ICON7 reported a hazard ratio for PFS of 0.71 (95% CI 0.58-0.86) (Martin et al. Gynecol Oncol. 2019;152:53-60) Increased OS • ICON7 reported a hazard ratio for OS of 0.78 (95% CI 0.63-0.97) among patients with high-risk ovarian cancer (Martin et al. 2019)
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.	

12. Sodium hypochlorite for treatment of eczema in cases with secondary bacterial infection

Application

12.1. The Committee noted that Pharmac sought updated advice from the Committee regarding sodium hypochlorite for eczema in cases with secondary bacterial infection.

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

Recommendation

12.3. The Committee **recommended** that sodium hypochlorite be funded in Section B of the Pharmaceutical Schedule with a **high priority**.

12.3.1. In making this recommendation, the Committee considered that funding sodium hypochlorite in the community would improve the safety of this treatment for patients with eczema with secondary bacterial infection and that engagement with healthcare providers for this patient population would convey other benefits.

Discussion

Māori impact

12.4. The Committee noted that eczema with secondary bacterial infection is more prevalent in Māori than non-Māori and that there is some evidence to suggest Māori may experience greater levels of *Staphylococcus aureus* colonisation than non-Māori. The Committee considered that the time required for topical treatment of bacterial colonisation also places a significant burden on whānau.

Background

12.5. The Committee noted that:

12.5.1. Sodium hypochlorite was previously included on the Community Schedule but was delisted in January 2011 due to very low volume usage and its low-cost availability in supermarkets.

12.5.2. Sodium hypochlorite was listed in the Hospital Medicines List (HML) following a positive recommendation from the Dermatology Subcommittee in 2013.

12.5.3. The Dermatology Subcommittee recommended sodium hypochlorite (possibly relating to community use) be funded in November 2015, however, PTAC in May 2016 disagreed with the recommendation and considered that simple bleach could be bought for a lower price than the prescription co-payment.

12.5.4. Pharmac received an application for the community schedule listing of sodium hypochlorite in August 2017. In June 2021, sodium hypochlorite was included in Pharmac's proposal to decline funding applications. Although no consultation feedback was received about it, it was not declined because Pharmac staff considered that this treatment would be mainly used in children and that there is no prescription co-payment on medicines or fees for general practice care for children aged 13 and under. Staff considered that further advice was warranted from PTAC, particularly on the equity issues associated with sodium hypochlorite.

Discussion

12.6. The Committee noted that eczema (also called atopic dermatitis) is characterised by dry itchy skin which can be erythematous and oozing in the acute phase and may become hyperpigmented, scaly and lichenified (thickened) when chronic. The Committee noted that patients with atopic dermatitis can experience a relapsing and remitting disease course and are at increased risk of cutaneous bacterial, viral, and fungal infections due to skin damage and complex interactions at the skin barrier.

12.7. The Committee was made aware of evidence that atopic dermatitis is reported in 15% of children aged between six and seven years of age, and in about 9% of adolescents aged between 13 and 14 years of age in New Zealand (Ab Hadi et al. Life (Basel). 2021;11:936). The Committee considered that atopic dermatitis improves/remits in about 75% of children or adolescents, particularly from six years of age.

12.8. The Committee noted that *Staphylococcus aureus (S. aureus)* colonisation is frequently identified and may be involved in the worsening of the disease. The Committee noted that up to 90% of adults with atopic eczema have been found to be colonised with large numbers of *S. aureus* on their skin (Leyden et al. Br J Dermatol 1974;90:525-30) and considered that greater density of colonisation is associated with worse disease. Members considered that *S. aureus* colonisation is less of an issue in adults compared with children, particularly from puberty onwards.

12.9. The Committee noted that two measures commonly used to estimate the affected surface area and intensity are the Eczema Area and Severity Index [EASI; range 0-72, minimal clinically important difference (MCID) 6.6] and the Scoring Atopic Dermatitis tool (SCORAD; range 0-103, MCID 8.7). The Committee considered that poor EASI or SCORAD scores show a strong correlation with greater extent of disease and worse health-related quality of life (HR-QOL) and was made aware of evidence that that *S. aureus* colonisation density and severity of SCORAD were weakly correlated in children of median age five years (Hill et al. Australas J Dermatol. 2011;52:27-31). However, members noted that these measures were designed for use in severe disease and do not correlate as well in more mild cases.

12.10. The Committee was made aware of evidence that atopic dermatitis is associated with a measurable decline in HR-QOL including psychological well-being and social function (Kiebert et al. Int J Dermatol. 2002;41:151-8) and that there is evidence of this correlation among children and adults (Maksimovic et al. J Dermatol. 2012;39:42-7). The Committee

considered that the patients with eczema with secondary bacterial infection/colonisation have a significant and severe health need due to the disease's symptoms and impact on QOL.

12.11. The Committee was made aware of evidence from a study of children 18 years or younger who attended a hospital dermatology clinic with atopic dermatitis, which reported a non-significant higher prevalence of *S. aureus* colonisation in Māori and Pacific children compared with non-Māori and non-Pacific children (Hill et al. 2011). The Committee considered it likely that eczema with secondary bacterial infection is more prevalent in Māori than non-Māori and that there is evidence to suggest Māori can experience greater levels of bacterial colonisation than non-Māori.

12.12. The Committee considered it was unclear from the evidence available whether atopic dermatitis disproportionately affects other ethnicities or other patient groups experiencing health disparities.

12.13. The Committee considered that the time required for topical treatment of bacterial colonisation places a large burden on family and whānau. The Committee was made aware of examples of evidence that atopic dermatitis has a significant impact on the family/whānau of children and infants with atopic dermatitis, correlating with disease severity according to SCORAD and with a greater impact for female children (Djurovic et al. Ital J Dermatol Venerol. 2021;156:29-35; Jang et al. Asia Pac Allergy. 2016;6:213–9; Djurovic et al. Postepy Dermatol Alergol. 2020;37:66-72).

12.14. The Committee noted that treatment focusses on bacterial decolonisation to reduce disease severity, and considered that while oral or topical antibiotics are available treatments, there is increasing concern about antimicrobial resistance worldwide. The Committee was made aware of New Zealand data reporting a 2% rate of antibiotic resistant *S. aureus* among children the group of 18 years or younger who attended a hospital dermatology clinic with atopic dermatitis (Hill et al. 2011). Members noted that the study did not report on the presence of methicillin-resistant *S. aureus* (MRSA), but considered that this would have occurred in very few cases due to strict topical antibiotic use.

12.15. The Committee noted that many publications from the past decade have reported on clinical trials of sodium hypochlorite (bleach) baths for atopic dermatitis, and considered that this area has been actively researched internationally due to community antimicrobial resistance from oral and topical antibiotics used for decolonisation. Members considered that the primary clinical effect of sodium hypochlorite is not necessarily to reduce the *S. aureus* infection, rather it causes a change in the skin barrier and reduces inflammation (and therefore is not as effective for treating furunculosis (boils)). Members considered the desire to minimise use of antibiotics in infants and children may have increased the interest in treatment with sodium hypochlorite baths.

12.16. The Committee was made aware of evidence from a Cochrane review of a wide range of interventions to reduce *S. aureus* in the management of eczema, in which the authors concluded that there was generally insufficient evidence to support any intervention to reduce colonisation, mostly in the form of small RCTs (George et al. Cochrane Database Syst Rev. 2019;2019:CD003871). The Committee was made aware that, of the five studies investigating sodium hypochlorite baths vs placebo, one reported no difference in colonisation and one reported no difference in HR-QOL, although the studies were deemed too small and poorly designed to draw strong conclusions about efficacy or safety.

12.17. The Committee was made aware of evidence from a systemic review of ten randomised controlled trials investigating sodium hypochlorite baths for atopic dermatitis (Bakaa et al. Ann Allergy Asthma Immunol. 2022;128:660-8.e9). The authors used a Bayesian approach and reported a reduction in EASI (ratio of means of EASI 0.78; 95% CI: 0.59 to 0.99), a reduction of *S. aureus* colonisation (risk ratio 0.89; 95% CI: 0.73 to 1.09), no

difference in adverse events or quality of life, and high uncertainty in the evidence. Members noted that the reduction in EASI was within the MCID and considered that the reduction in colonisation probably occurs despite the results crossing the line of significance.

12.18. The Committee noted evidence from a blinded, randomised, controlled trial investigating treatment of *S. aureus* with intranasal mupirocin and sodium hypochlorite baths (two times per week) in 31 participants aged 6 months to 17 years with moderate-severe AD (Huang et al. Pediatrics. 2009;123:e808-14), as an example of one of the studies included in the meta-analyses. The Committee noted that the authors reported a reduction in EASI scores for bath-submerged sites at one- and three-months post-treatment vs placebo and reduced prevalence of MRSA vs a general hospital population with *S. aureus* skin colonisation (~7% v ~80%).

12.19. The Committee noted evidence from a randomised, placebo-controlled, crossover trial of sodium hypochlorite baths for 40 patients aged four to 18 years with moderate to severe eczema (Hon et al. J Dermatolog Treat. 2016;27:156-62). The Committee noted that there was no significant impact of sodium hypochlorite baths on colonisation but that water baths were associated with improved SCORAD in the intention-to-treat analysis. The Committee noted that a within-group analysis reported sodium hypochlorite baths were associated with a reduction in topical corticosteroid and antibiotic use. Members considered that the methodology was fairly typical of studies in this context and that the crossover study design would have been impeded by the carryover effect of treatment.

12.20. The Committee also noted the following evidence:

- Wong et al. J Dermatol. 2013;40):874-80
- Gonzalez et al. J Am Acad Dermatol. 2016;75:481-93
- Chopra R. Ann Allergy Asthma Immunol. 2017;119:435

12.21. Overall, the Committee considered that there was an abundance of evidence for sodium hypochlorite baths in the treatment of atopic eczema. The Committee considered that there was a benefit of sodium hypochlorite baths compared with oral antibiotics from a reduced risk of antimicrobial resistance and specifically MRSA.

12.22. The Committee considered that the key concern with sodium hypochlorite baths is safety, and that standardised dosing would improve patient safety. The Committee noted that bleach products available at supermarkets come in various concentrations. The sizes of baths are variable making it difficult to dilute bleach correctly. It was also noted that bleach products can include other ingredients (eg gels and surfactants) which may be irritating to the skin or have unknown impacts on sodium hypochlorite release. Members noted that not all households have a bath available, although large buckets placed in the shower are sometimes used for children in homes where baths are not available. It was also noted that the cost of hot water limited access to treatment, and that due to this in some cases multiple children will bathe in the sodium hypochlorite bath, rather than just the individual, which may confer protection from bacterial-related skin infection to other children in the whānau. The Committee noted that sodium hypochlorite can degrade over a relatively short period of time, and considered this could be better managed with a funded product with standardised expiration and a lower volume. The Committee considered that standardised concentrations and dosing should be considered for a funded product, as fixed volumes and concentrated solutions would allow for standardised instructions, although it was unclear whether a range of strengths or concentrations would need to be funded. The Committee acknowledged that clear instructions on usage and the availability of a bathtub would also be required, although members considered it may be feasible to apply using a sponge followed by rinsing off in a shower.

12.23. The Committee considered that funding sodium hypochlorite would convey benefits from engagement with a primary healthcare provider through education on optimal management and safety, including instructions for sodium hypochlorite use and dose standardisation. The Committee noted that the co-payment for sodium hypochlorite would not be applicable for young children and that children are eligible for free GP visits, but acknowledged that there may be other barriers to visiting a GP, including unavailability of appointment, patient time, and rural location. The Committee considered that funding sodium hypochlorite for community use might improve equity but acknowledged that this may be limited given there is no prescription co-payment on medicines or fees for general practice care for children aged 13 and under.

12.24. The Committee considered that funding sodium hypochlorite was unlikely to create any significant changes in health sector expenditure, although it was unclear who would prepare the product in a standardised concentration. The Committee considered it was unclear what impact funding sodium hypochlorite via the community Schedule would have on its usage in hospitals, and considered that Pharmac could seek a view on this from the Dermatology Advisory Committee if this was pertinent. It was noted that some hospitals also use potassium permanganate.

12.25. The Committee considered that sodium hypochlorite would be used for as long as required until another intervention is needed, and considered that adults were more likely to use other options such as oral or topical antibiotics. The Committee considered that sodium hypochlorite would replace oral or topical antibiotics, and might replace or be used in combination with a funded topical corticosteroid. The Committee considered that Pharmac could include other decolonisation such as oral or topical antibiotics as a comparator for its assessment, although it was noted that there has been a shift away from the use of oral antibiotics for decolonisation in recent years. The Committee considered that use of sodium hypochlorite baths in patients with a history of recurrent infections was not relevant given the focus was on decolonisation. The Committee considered that a reduction in antibiotic resistance would also be a relevant and important outcome for New Zealand, although this would be hard to quantify for assessment.

12.26. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for sodium hypochlorite if it were to be funded in New Zealand for atopic dermatitis. 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 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	Patients with moderate to severe atopic dermatitis
Intervention	Sodium hypochlorite diluted in a bath 2 times per week
Comparator(s)	Other decolonisation treatments ie oral or topical antibiotics
Outcome(s)	Reduced clinical severity of eczema
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.	