PTAC Pharmacology and Therapeutics Advisory Committee

Objective advice to PHARMAC

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Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 18 & 19 November 2021

This meeting was held via Zoom

The records of PTAC and Subcommittees of PTAC are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and Specialist Advisory Committees July 2021. Note that this document is not necessarily a complete record of the meeting; only the relevant portions of the record relating to discussions about an application or Pharmac staff proposal that contain a recommendation are generally published.

PTAC and Specialist Advisory Committees may:

a) recommend that a pharmaceutical be listed by Pharmac on the Pharmaceutical Schedule and the priority it gives to such a listing;

b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

c) recommend that Pharmac decline to list a pharmaceutical on the Pharmaceutical Schedule

Pharmac is not bound to follow the recommendations made below. Applications are prioritised by Pharmac against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or any Specialist Advisory Committee, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

Present:

PTAC members:
Mark Weatherall (Chair)
Marius Rademaker (Deputy Chair)
Alan Fraser
Brian Anderson
Giles Newton Howes
Jane Thomas
Jennifer Martin
Lisa Stamp
Matthew Strother
Rhiannon Braund
Sean Hanna
Simon Wynn Thomas
Stephen Munn
Tim Stokes

Apologies:
Bruce King
Elizabeth Dennett

Guests:
Robyn Manuel (CAC observer)
Hazel Heal (CAC observer)

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

1.1. This meeting record of PTAC is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) July 2021, available on the Pharmac website at Pharmacology and Therapeutics Advisory Committee (PTAC) Terms of Reference July 2021 - Pharmac | New Zealand Government

1.2. 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.

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

1.4. 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.

2. Record of PTAC meeting held 18 & 19 August 2021

2.1. The Committee reviewed the record of the PTAC meeting held on 19 & 20 August 2021

2.2. The Committee accepted the record.

3. Subcommittee Records

Rare Disorders and Neurological Subcommittee record review

3.1.1. The Committee noted the record and recommendations of the joint Rare Disorders and Neurological Subcommittees meeting held in July 2021.

3.1.2. The Committee noted that PTAC has since considered the funding application for risdiplam for SMA (in August 2021) following the Subcommittees' review and made its own recommendations.

CaTSoP record review

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

3.1.4. With regard to item 4, the Committee noted the Subcommittee's comments about possible alternatives for mitomycin and noted the presence of early trials indicating gemcitabine may have an effect in similar patient populations, and considered this could be an alternative, if required. The Committee considered advice should still be sought as recommended by the Subcommittee to confirm what acceptable alternatives are available, if required to meet patient needs.

3.1.5. With regard to item 7 and Cancer Treatment Subcommittee's (CaTSoP) consideration of daratumumab in combination with bortezomib and dexamethasone

for the treatment of patients with multiple myeloma who have received one prior line of therapy:

3.1.5.1. The Committee noted CaTSoP's recommendation to list both formulations of daratumumab with a high priority and its previous support for a recommendation to list daratumumab. The Committee considered that there remained uncertainty regarding the overall survival benefit of daratumumab in this patient population. The Committee considered that there also remained uncertainty regarding the quality of life benefit from the addition of daratumumab to bortezomib and dexamethasone from the CASTOR trial (Hungria V et al. Br. J. Haematol. 2021 193: 561-569). The Committee considered that if Pharmac required further advice to inform modelling then this could be sought from PTAC and reiterated its support for funding with a low priority pending published evidence supporting survival benefit of daratumumab.

3.1.5.2. The Committee considered that it was reasonable to consider that subcutaneous daratumumab would be similarly efficacious to that of intravenous daratumumab based on the results from the non-inferiority COLUMBA trial of subcutaneous daratumumab compared to intravenous daratumumab in patients with multiply relapsed multiple myeloma (Mateos et al. Lancet Haematol. 2020;7:e370-e380).

3.1.6. With regard to item 8 and CaTSoP's consideration of pembrolizumab for the treatment of patients with relapsed or refractory Hodgkin lymphoma:

3.1.6.1. The Committee noted CaTSoP's recommendation to list pembrolizumab with a high priority. The Committee considered that there was uncertainty regarding the overall survival benefit from treatment with pembrolizumab for this patient group based on the results from the KEYNOTE-204 trial (Kuruvilla et al. Lancet Oncol. 2021;22:512-24). The Committee however acknowledged that there appeared to be a high correlation between progression free survival and overall survival for patients with relapsed or refractory Hodgkin lymphoma and considered that this trial provided evidence of a progression free survival benefit compared to brentuximab vedotin, and that the benefit would be greater in New Zealand where brentuximab vedotin is not funded.

3.1.7. With regard to item 9 and CaTSoP's consideration of pembrolizumab for the first line treatment of microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) unresectable or metastatic colorectal cancer treatment, and the treatment of unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancers that have progressed following prior treatment:

3.1.7.1. The Committee noted the use of pembrolizumab in colorectal cancer and considered this was a high health need patient population, with the primary evidence (KEYNOTE-177) showing evidence of survival benefit and quality of life improvement. The Committee supported the recommendation for funding with a high priority.

3.1.7.2. The Committee noted the application for use of pembrolizumab second line for all MSI-H/ dMMR cancers and supported the Subcommittee's recommendation to defer making a recommendation pending further evidence, noting the available evidence was limited to a basket trial in a range of individual tumour entities.

3.1.8. With regard to item 10 and CaTSoP's consideration of niraparib for ovarian, fallopian tube or primary peritoneal cancer, advanced high-grade, first and second-line, platinum-sensitive maintenance treatment:

3.1.8.1. The Committee noted the indication from CaTSoP that there was a likely class effect across the various Poly (ADP-ribose) polymerase (PARP) inhibitors with no preferred agent identified, noting there are different diagnostic tests associated with each when limiting treatment to breast cancer susceptibility gene mutation (BRCAm) or homologous recombination deficiency (HRD) patient populations and differential costs associated with each agent and test. The Committee considered the cost of testing may have an impact on the cost-effectiveness of the different PARP inhibitors for these patient populations.

3.1.8.2. The Committee noted the evidence supporting the use of niraparib included the broader patient population (i.e 'all comers'). The Committee supported the recommendations made by the Subcommittee for the use of niraparib in the BRCAm, HRD and all comers populations.

3.1.9. With regard to item 12 and CaTSoP's consideration of nab-paclitaxel for the treatment of metastatic breast cancer:

3.1.9.1. The Committee noted there was likely to be a small number of patients with a contraindication to taxanes (eg paclitaxel) that would benefit the most from nab-paclitaxel treatment. The Committee noted concern regarding the definition of 'contraindication' and considered that historically it has been difficult to define 'contraindication' sufficiently to ensure appropriate targeting of a patient population most likely to benefit from nab-paclitaxel treatment.

3.1.9.2. The Committee noted the Subcommittee's comments regarding the evidence of improved tolerance to nab-paclitaxel treatment, and likely cost benefits associated with infusion time reductions. The Committee noted the meta-analysis comparing the efficacy and safety of nab-paclitaxel chemotherapy compared with solvent-based-taxanes (Lee et al. Sci Rep. 2020;10:530) and considered this showed a slight overall survival benefit; however considered the majority of evidence indicated nab-paclitaxel to be non-inferior to paclitaxel. The Committee considered the primary benefit for the broader metastatic breast cancer population was the reduced infusion requirements associated with nab-paclitaxel, noting many infusion centres were at, or near, capacity.

3.1.9.3. The Committee noted the Subcommittee's recommendation for nab-paclitaxel treatment for metastatic breast cancer with a history of hypersensitivity reactions, or contraindication. The Committee retained it's 2019 recommendation for funding of nab-paclitaxel for metastatic breast cancer if cost-neutral to paclitaxel (including relevant health system costs).

3.1.10. With regard to item 13 and CaTSoP's consideration of atezolizumab in combination with bevacizumab for the treatment of patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy:

3.1.10.1. The Committee noted the available evidence reported effect compared to sorafenib which is not funded in New Zealand and considered that an indirect comparator analysis would be required to understand the likely benefit of treatment in the New Zealand setting. The Committee noted sorafenib has some benefit over best supportive care but considered this to be limited, and considered that based on the IM-BRAVE trial (Finn et al. N Engl J Med. 2020;382:1894-1905) atezolizumab provided a survival benefit for which the impact for New Zealand patients was likely underestimated as comparison would be to best supportive care.

3.1.10.2. The Committee noted the Subcommittee's recommendations and considered that if any further information based on the extrapolation of benefit

from different trials were required to inform modelling, then further review by CaTSoP could be considered.

3.1.11. The Committee noted and agreed with the Subcommittee's remaining recorded considerations from the July 2021 meeting.

Mental Health Advisory Committee record review

3.1.12. The Committee noted the record and recommendations of the Mental Health Advisory Committee meeting held in September 2021.

3.1.13. The Committee noted that the Advisory Committee recommended aripiprazole depot be funded with a medium priority, as an update from PTAC's 2015 cost-neutral recommendation. The Committee noted that additional evidence has since become available to inform this updated recommendation.

3.1.14. Buprenorphine depot

3.1.14.1. The Committee noted that the Advisory Committee recommended buprenorphine depot be funded with a high priority for opioid use disorder. The Committee **recommended** that this application also be shared with the Analgesic Advisory Committee given opioid addiction may coexist in patients with chronic pain.

3.1.14.2. The Committee considered that there are access issues in New Zealand to both chronic pain management and addiction support services. Members considered this was a sector-wide issue, extending beyond pharmaceutical funding.

3.1.15. The Committee noted the Advisory Committee's recommendation that lisdexamfetamine should be funded only if cost neutral to the Concerta brand of extended-release methylphenidate.

Ad-hoc Rheumatology Advisory Committee record review

3.1.16. The Committee noted the record of the Ad-hoc Rheumatology Advisory Committee meeting held in August 2021.

3.1.17. The Committee noted the meeting was in response to an imminent tocilizumab stock shortage and that Pharmac staff had sought urgent expert advice from the Advisory Committee regarding this issue and potential alternatives for patients. The Rheumatology Advisory Committee considered a JAK inhibitor (eg upadacitinib or tofacitinib) would be a suitable alternative for rheumatoid arthritis patients with no alternative treatment options. The Committee noted Pharmac subsequently made a decision to fund upadacitinib for patients with rheumatoid arthritis, to help manage the tocilizumab stock shortage and provide patients with a suitable treatment option.

3.1.18. The Committee noted no formal recommendations were made at the meeting.

7. Correspondence & Matters Arising

Trastuzumab treatment for metastatic breast cancer following treatment with trastuzumab emtansine (T-DM1) in the neoadjuvant setting

Discussion

7.1.1. The Committee noted that in August 2020, PTAC reviewed an application for trastuzumab emtansine (T-DM1) for the treatment of HER2 positive early breast cancer in patients who have residual disease after neoadjuvant systemic treatment

that included HER2-targeted therapy. PTAC recommended that T-DM1 be listed with a low priority and suggested further advice be sought from CaTSoP, including advice on treatment sequencing with trastuzumab in the treatment of metastatic breast cancer, if trastuzumab emtansine were available for use in the adjuvant setting.

7.1.2. The Committee noted that CaTSoP reviewed the application in October 2020 and recommended T-DM1 be funded for this indication with a high priority. The Subcommittee made this recommendation based on the high quality of evidence of benefit, prevention of relapse, and the curative intent of treatment with T-DM1 in this setting but considered that the unmet health need for these patients is not high as they already have relatively good prognosis from currently available funded treatments.

7.1.3. The Committee noted that PTAC subsequently reviewed the record of CaTSoP's October 2020 discussion in February 2021 and considered that there remained uncertainty regarding the use of trastuzumab in the metastatic setting following prior use of T-DM1 in the adjuvant setting. The Committee considered that if adjuvant T-DM1 were to be funded then the Special Authority criteria for trastuzumab should exclude re-treatment in the metastatic setting for patients previously treated with adjuvant trastuzumab emtansine. The Committee considered that if there was a group of patients who would benefit from trastuzumab in the metastatic setting after adjuvant T-DM1 then this group would need to be clearly defined and further advice should be sought from CaTSoP regarding this.

7.1.4. The Committee noted that feedback had been provided by a member of CaTSoP clarifying the consideration that patients would have access to T-DM1 once in their treatment journey (either in the adjuvant, or metastatic setting), but that this does not apply to access to trastuzumab where treatment with trastuzumab would be expected to remain as per status quo, available in the adjuvant/neoadjuvant and metastatic setting.

7.1.5. The Committee considered that access criteria should prevent access to T-DM1 multiple times in a patient's treatment journey as there is currently a lack of evidence supporting efficacy in this context. The Committee noted evidence from the phase III CLEOPATRA randomised control trial indicating benefit with re-treatment of trastuzumab in the metastatic setting (Swain, MD et al. N Engl J Med. 2015; 372:724-734) and considered that access to trastuzumab could remain unchanged and aligned with CaTSoP's recommendation.

Capsaicin 0.075% cream for cannabinoid hyperemesis syndrome

Recommendation

7.1.6. The Committee **recommended** that capsaicin cream 0.075% for the treatment of cannabinoid hyperemesis syndrome be declined, based on limited evidence of benefit.

Discussion

7.1.7. The Committee considered correspondence submitted from a DHB pharmacist relating to a funding application for capsaicin 0.075% cream for cannabinoid hyperemesis syndrome. The Committee noted it had previously considered this application at its meeting in May 2019 and had recommended it be declined based on limited evidence of benefit, an unclear mechanism of action, and availability of funded alternatives.

7.1.8. The Committee noted that the applicant had provided updated evidence (Dean et al. Acad Emerg Med. 2020 Nov;27(11):1166-1172), that had been published after its meeting in May 2019.

7.1.8.1. The Committee considered the publication by Dean et al. (Acad Emerg Med. 2020), a randomized, double-blind, placebo-controlled trial for capsaicin 0.075% cream for the treatment of cannabinoid hyperemesis syndrome (CHS).

7.1.8.2. The Committee noted the trial enrolled 30 patients, 17 in the capsaicin arm and 13 in the placebo arm. The primary outcome was the severity of nausea on a visual analog scale (VAS), and the authors reported a reduction of mean nausea severity of 6.4 ± 2.8 cm versus 3.2 ± 3.2 cm (difference -3.2 cm, 95% CI, -0.9 to -5.4 cm) at 60 minutes post treatment. The Committee noted there was no significant difference in the mean nausea score at the 30-minute interval, with a mean nausea severity of 4.1 ± 2.3 cm in the capsaicin arm, and 6.1 ± 3.3 cm in the placebo arm (difference -2.0 cm, 95% CI, 0.2 to -4.2 cm). The Committee noted overlapping confidence intervals and that a higher proportion of the treatment group had complete cessation of nausea (29.4% vs. 0%).

7.1.8.3. The Committee considered that even though the study was designed as a randomized double-blind placebo-controlled trial that it would have been difficult to control for the burning and/or itching that may occur when the product is applied.

7.1.9. The Committee noted a retrospective study (Lee et al. Ann Pharmacother. 2021 May 17;10600280211018516) that investigated the use of capsaicin cream in patients presenting to the emergency department (ED) with suspected CHS. The authors of the study reported a median pain score decrease from 8 [IQR, 2-9] to 5.5 [IQR, 0-8]. The Committee considered that despite treatment with capsaicin cream, further treatment was required in 58% of participants.

7.1.10. The Committee noted a single-centre retrospective study (Kum et al. Am J Emerg Med. 2021 Nov;49:343-351) that evaluated the efficacy of capsaicin in patients presenting to the ED with suspected or confirmed CHS. The Committee noted the authors reported the treatment group using 0.025% capsaicin cream achieved 58% efficacy, defined as only requiring ≤1 rescue medication for symptom relief after capsaicin treatment, compared to 21% in the patient group without capsaicin. A secondary outcome of time to discharge after administration was 3.7 hours in the treatment group compared to 6.1 hours without capsaicin.

7.1.11. The Committee considered a retrospective cohort analysis (Wagner et al. Clin Toxicol (Phila). 2020 Jun;58(6):471-475) that evaluated the safety and efficacy of topical capsaicin (multiple concentrations) for patients presenting with cannabinoid hyperemesis syndrome. The Committee noted that the authors reported the length of stay (LOS) in ED decreased by 22 minutes with capsaicin treatment.

7.1.12. The Committee considered that in the NZ context patients who present to ED are repeatedly admitted (~4 months between visits), and often present with recurrent abdominal symptoms and use of recreational drugs. However, the Committee considered that it had not seen robust evidence to support that treatment with capsaicin cream 0.075% would have an effect on the number of presentations, time in hospital, or reduction in symptoms.

7.1.13. The Committee considered that its previous estimated patient numbers of 2,000-3,000 per year were likely an overestimate and that the Pharmac staff estimate of 1,000 patients per year seemed more realistic.

7.1.14. Overall, the Committee considered that there was a lack of consensus on the definition for CHS between studies and considered that clinically meaningful benefits were uncertain based on the low quality and low strength of evidence. The Committee considered that it is an area of emerging research and would be happy to review the application should new evidence become available.

7.1.15. The Committee considered that the price of capsaicin was approximately $12 per tube and that the impact to the Combined Pharmaceutical Budget if capsaicin cream was to be funded for CHS would likely be low. However, the Committee considered that due to the poor quality of evidence that its recommendation for the application to be declined remained.

7.1.16. The Committee noted that the applicant's DHB was considering running a trial to investigate the use of capsaicin cream for the treatment of CHS in the NZ population and that it would be happy to review the results from the trial once available.

8. Daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone (D-VCd) for the treatment of newly diagnosed systemic light chain (AL) amyloidosis

Application

8.1. The Committee reviewed the application from Janssen for subcutaneous daratumumab (Darzalex) in combination with bortezomib, cyclophosphamide and dexamethasone (D-CyBorD) for the treatment of newly diagnosed systemic light chain (AL) amyloidosis.

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 daratumumab (intravenous or subcutaneous) in combination with bortezomib, cyclophosphamide and dexamethasone (D-CyBorD) be funded for the treatment of newly diagnosed systemic light chain (AL) amyloidosis with a **medium priority**, subject to Special Authority criteria:

DARATUMUMAB
Initial application – (AL amyloidosis) only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months or applications meeting the following criteria.
All of the following:
1. Patient has previously untreated systemic AL amyloidosis; and regard
2. Daratumumab is to be used in combination with bortezomib, cyclophosphamide and dexamethasone for week 1 to 24 and as a monotherapy from week 25 until disease progression.

Renewal – (AL amyloidosis) only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months.
All of the following:
1. No evidence of disease progression; and
2. The treatment remains appropriate, and the patient is benefitting from treatment.

8.4. In making this recommendation, the Committee considered:

8.4.1. the high health need of patients with AL amyloidosis due to high morbidity and mortality

8.4.2. the good quality evidence of rapid and deep haematologic complete response or very good partial response with the addition of daratumumab in the ANDROMEDA trial

8.4.3. the limited evidence for overall survival and quality of life with the proposed regimen.

8.5. The Committee considered that Pharmac should seek advice from the Cancer Treatments Advisory Committee regarding appropriate stopping criteria that Pharmac could use, and their view of using a 12-month duration of approval, in the Special Authority criteria for daratumumab for AL amyloidosis.

Discussion

8.6. The Committee noted that systemic AL (light chain) amyloidosis is a rare, acquired, incurable, life-threatening heterogenous disease characterised by the clonal proliferation of CD38+ plasma cells throughout the body. The Committee noted that these clones produce misfolded immunoglobulin light chains that aggregate into amyloid protein deposits (insoluble fibrils) within organs causing organ dysfunction, progressive disability, and death (mainly driven by cardiac disease). The Committee noted that AL amyloidosis is rare but considered that it doesn't meet Pharmac's Policy principles for rare disorders.

8.7. The Committee noted that patients with abnormal immunoglobulins identified may experience a challenging diagnostic process, often resulting in delayed start to treatment. The Committee noted that the average age at diagnosis is 63 years and the most frequently affected organs are the heart (in 70–80% of patients) and kidneys (in 50–60% of patients) (Muchtar et al. J Intern Med. 2021;289:268-92). The Committee noted that there is usually multi-organ involvement also at diagnosis, leading to worse prognosis and earlier death (Oubari et al. Eur J Haematol. [Epub ahead of print] 2021. [cited 16 2021 Aug 16]). The Committee considered that patients with AL amyloidosis in New Zealand would likely present later than international cases, and would generally have more than one organ involved at presentation, and may be very ill at diagnosis.

8.8. The Committee noted that treatment for AL amyloidosis aims to rapidly achieve a deep and durable response, with early treatment intending to avoid irreversible organ damage from fibrils (Al Hamed et al. Blood Cancer J. 2021;11:97). The Committee considered that prognosis and survival in AL amyloidosis appear to depend on treatment efficacy, which is assessed in the clinical trial evidence using a range of measures including haematological response (which consists of the removal of free light-chain proteins in plasma) and a range of organ-related measures (such as N-terminal pro-B type natriuretic peptide (NT-proBNP) level. The Committee considered that haematological response in particular appeared to be predictive of survival in AL amyloidosis.

8.9. The Committee noted that treatments used for AL amyloidosis are in many cases derived from those used in other plasma cell disorders, such as multiple myeloma, and are used as lines of therapy with the potential for retreatment using the same treatment/regimen if a patient responded well to it previously. The Committee considered that in AL amyloidosis, as in multiple myeloma, there are diminishing benefits with each subsequent line of treatment although survival data for treatments for AL amyloidosis is confounded by their use as retreatment. However, the Committee noted that survival of patients with AL amyloidosis had increased over recent cohorts due to the availability of newer, more effective treatments for multiple myeloma and AL amyloidosis (eg bortezomib).

8.10. The Committee noted that the choice of treatment for AL amyloidosis depends on prognostic patient characteristics including age, frailty, comorbidities, cardiac status, organ involvement, cytogenetics and ECOG performance status. The Committee noted that bortezomib is funded for patients with AL amyloidosis subject to Special Authority criteria and that it rapidly reduces light chains. The Committee noted that thalidomide is also funded for systemic AL amyloidosis subject to Special Authority criteria. The Committee noted that the preferred first-line treatment regimen consists of bortezomib, cyclophosphamide and dexamethasone (CyBorD) used in about 75% of New Zealand cases, while cyclophosphamide, thalidomide and dexamethasone (CTD) or melphalan with dexamethasone are used in about 25%. The Committee considered that about 36% of patients would be expected to discontinue CyBorD early but that only about 4% of those might be due to toxicity, with other reasons to discontinue being death, proceeding to autologous stem cell transplant (ASCT), or undergoing other therapies.

8.11. The Committee considered that only about 10% of patients with AL amyloidosis in New Zealand would be suitable candidates for ASCT, with or without bortezomib-based induction therapy, if performed early in cases without significant organ damage. The

Committee considered that the few patients who received ASCT might have improved survival and was made aware of evidence reporting that, of those who had survived for at least ten years post-diagnosis, 47% remained treatment-free (Muchtar et al. Br J Haematol. 2019;187:588-94). The Committee noted that, for the majority who are ineligible for ASCT, bortezomib plays a key role in early treatment. The Committee noted that about one third of patients die within one year of diagnosis and four-year survival is 54% (Muchtar E, et al. Blood 2017;129:2111-9). The Committee noted that patients with Mayo 2004 stage IIIa cardiac disease receive a benefit from bortezomib-containing regimens (median overall survival [OS] of patients with IIIa disease was 25.9 months) but that there is a poor prognosis for Mayo stage IIIb disease (3.5 months). Overall, the Committee considered that patients with AL amyloidosis have a high health need despite currently funded treatments.

8.12. The Committee noted that daratumumab is an IgG1κ human monoclonal antibody that binds to the CD38 protein expressed at a high level on the surface of clonal plasma cells in AL amyloidosis. The Committee noted that daratumumab rapidly decreases fibril deposits in organs in AL amyloidosis by inducing cell death in the fibril-producing clonal plasma cells, and that its direct actions on clonal plasma cells and immunomodulatory actions may contribute to rapid, deep and durable response to treatment.

8.13. The Committee noted that daratumumab had recently been considered by CaTSoP in July 2021 for the following two applications:

- Intravenous daratumumab in combination with bortezomib and dexamethasone for relapsed/refractory multiple myeloma
- Subcutaneous daratumumab for multiple myeloma

8.14. The Committee noted that daratumumab, which is available in intravenous (IV) or subcutaneous (SC) formulations, is Medsafe-approved for newly diagnosed multiple myeloma and relapsed/refractory multiple myeloma indications (IV and SC formulations) and Medsafe has received an application for daratumumab for AL amyloidosis (SC formulation only). The Committee noted that in July 2021, CaTSoP considered that there was no evidence to suggest that efficacy outcomes with daratumumab SC would be any different to those with daratumumab IV based on the evidence from the COLUMBA non-inferiority trial (Mateos et al. Lancet Haematol. 2020;7:e370-e380).

8.15. The Committee noted the recommended dose of daratumumab SC for AL amyloidosis is a flat dose of 1800 mg given as a subcutaneous injection weekly for weeks 1-8, every 2 weeks for weeks 9-24, and then every four weeks from weeks 25 onwards until disease progression. The Committee noted that the application proposes that daratumumab SC is used in combination with CyBorD (VCd) therapy, consisting of bortezomib 1.3 mg/m2 SC; cyclophosphamide 300 mg/m2 oral or IV; dexamethasone 40 mg oral or IV on days 1, 8, 15, 22 in every 28-day cycle for a maximum of 6 cycles (ie up to week 24).

8.16. The Committee noted that the key evidence for daratumumab SC in AL amyloidosis comes from the randomised (1:1), open-label, active-controlled, multicentre, phase III ANDROMEDA study of 388 patients with newly diagnosed AL amyloidosis with at least one organ impacted, cardiac stage I-IIIA disease (Mayo 2004) and eGFR of at least 20 mL/min/1.73m^2 (Kastritis et al. N Engl J Med 2021; 385:46-58; Kastritis et al. Presented at the 25th European Haematology Association (EHA25) Annual Congress 2020; Abstract Nr LB2604). The Committee noted that participants received either D-VCd consisting of daratumumab SC 1800 mg weekly for cycles 1-2, then 2-weekly for cycles 3-6, with VCd (CyBorD) weekly for 6 cycles, then maintenance with daratumumab SC 1800 mg 4-weekly until major organ deterioration-progression free survival (PFS) for maximum 24 cycles; or VCd (CyBorD) weekly for 6 cycles, then observation until major organ deterioration-PFS.

8.17. The Committee noted that the median age of ANDROMEDA participants was 64 years and at least two organs were affected in about two thirds of patients. The Committee noted that patient characteristics were generally balanced between groups although one D-VCd patient and three VCd patients had stage IIIb disease and ten D-VCd patients and eight VCd patients had ECOG performance status scores of two, rather than ECOG of zero to one.

8.18. The Committee noted that the primary endpoint in ANDROMEDA was overall haematologic complete response and that a haematologic complete response (CR) was defined as normalisation of free light chain (FLC) levels and involved FLC ratio, and negative serum and urine immunofixation. The Committee noted that after median follow-up of 11.4 months, the overall haematologic response rate was 53.3% with D-VCd vs 18.1% with VCd with a relative risk ratio of 2.9 (95% CI: 2.1 to 4.1) and odds ratio of 5.1 (95% CI: 3.2 to 8.2; P<0.001 for both comparisons). The Committee noted that a very good partial response (VGPR) was defined as either a reduction in the difference between involved and uninvolved FLC (dFLC) of <40 mg/L from baseline dFLC of at least 50 mg/L, or at least a 90% reduction in serum M-protein if baseline dFLC was less than 50 mg/L. The Committee noted that the median time to a VGPR or CR among responders was 17 and 60 days, respectively, with D-VCd and 25 and 85 days, respectively, with VCd.

8.19. The Committee noted that the composite endpoint of major organ deterioration– PFS in ANDROMEDA was reported to be improved with D-VCd compared with VCd, hazard ratio (HR) 0.58 (95% CI: 0.36 to 0.93; P=0.0224). The Committee noted that the six-month cardiac response rate was 42% with D-VCd compared with 22% with VCd (P=0.0029), and the six-month renal response rate was 54% and 27%, respectively (P<0.0001).

8.20. The Committee noted the updated results of the ANDROMEDA study after median of 20.3 months follow-up were presented at the American Society of Clinical Oncology (ASCO) conference in June 2021 (Kastritis et al. J Clin Oncol. 2021;39(15_suppl):8003). The Committee noted that the primary endpoint of haematologic complete response rate remained significantly higher with D-VCd (59%) than VCd (19%); odds ratio 5.9 (95% CI: 3.7 to 9.4; P<0.0001) and that haematologic CR rates were high across all prespecified subgroups except baseline renal stage III disease and race other than white or Asian for which 95% CIs crossed one. The Committee noted that at least a VGPR was reported in 79% with D-VCd vs 50% with VCd (odds ratio 3.7; 95% CI:2.4 to 5.9; P<0.0001) and that among at least VGPR responders, the median time to VGPR or better was 0.56 months with D-VCd (N=154) vs 0.82 months with VCd (N=97). The Committee considered that this provided evidence of a good improvement in haematologic response in the relevant patient group with this disease.

8.21. The Committee noted that the rates of cardiac response (based on NT-proBNP response) after longer follow-up in ANDROMEDA were 42% and 57% with D-VCd at 6 and 12 months, respectively, vs 22% and 28% with VCd at 6 and 12 months, respectively. The Committee noted that the odds ratio for cardiac response rate at 12 months was 3.5 (95% CI 2.0 to 6.2; P<0.0001). The Committee noted that renal response was defined as at least a 30% decrease in proteinuria or drop in proteinuria below 0.5 g/24 hours in the absence of renal progression. The Committee noted that renal response rates with longer follow-up were 57% with D-VCd vs 27% with VCd at 12 months (odds ratio 4.1; 95% CI 2.3 to 7.3; P<0.0001). The Committee considered that this was evidence of some improvement but that the magnitude of benefit was uncertain given the endpoints used markers of response instead of objective measures of organ function. The Committee considered that the addition of daratumumab to VCd was unlikely to improve rates of renal transplant in New Zealand patients diagnosed with AL amyloidosis, as most would be diagnosed at a late stage in the disease course. Members considered that the exception might possibly be in patients with the least severe disease (eg those with disease in a single kidney, good heart health, who may have good survival to two years and could be candidates for transplant at that time).

8.22. The Committee noted that infection was reported in 13% of ANDROMEDA participants who received D-VCd vs 9% who received VCd and considered that this was a slight increase associated with daratumumab. The Committee noted that systemic administration-related reactions to daratumumab were reported in 7.3% of D-VCd participants and that most reactions occurred at the first administration of daratumumab.

8.23. The Committee noted that overall survival (OS) in ANDROMEDA did not differ substantially between the two groups after median follow-up of 11.4 months (hazard ratio for death, 0.90; 95% CI: 0.53 to 1.53; Figure S4, Supplementary Appendix to Kastritis et al. N Engl J Med 2021; 385:46-58). The Committee noted that 31 deaths (16%) were reported with D-VCd vs 40 deaths (21%) with VCd after median of 20.3 months follow-up [Kastritis et al. J Clin Oncol. 2021; 39(15_suppl):8003]. The Committee considered that mortality was not substantially different between groups and was not statistically significant, however, the Committee noted a small number of patients contributed survival data to 20 months and therefore considered that it was not appropriate to extrapolate from beyond about 15 months. Members noted the 84% of ANDROMEDA D-VCd patients alive at 20 months was a higher proportion than the 66% of patients with AL amyloidosis reported to be alive after one year in the retrospective study by Muchtar et al. (Blood 2017;129:2111-9), although these figures could be influenced by differences between the characteristics of the respective populations. The Committee considered that it was unlikely that good quality OS data would occur in this setting due to the effects of subsequent treatment for patients who received CyBorD, including possible retreatment with previously used regimens.

8.24. The Committee noted that patient-reported outcomes were assessed on day one of cycles one to six for both treatment groups in ANDROMEDA and every eight weeks thereafter in the D-VCd group, and that these health-related quality of life (HRQOL) data were presented as a conference abstract (Sanchorawala et al. Presented at the American Society of Haematology (ASH) Annual Meeting and Exposition 2020; Abstract Nr 1640). The Committee considered that despite not being reported in a peer-reviewed journal, the HRQOL data from a wide range of measures were informative and appeared to show real differences in treatment effect between groups. However, the Committee noted that HRQOL data was not collected for the VCd group beyond six months and considered that made it challenging to delineate between improvements in HRQOL from D-VCd treatment and improvement resulting from bortezomib discontinuation after six months in both groups. The Committee noted that improvements in the EORTC-QLQ-C30 global health score and fatigue score were reported with both D-VCd and VCd up until cycle six, and that both measures then improved beyond cycle six with D-VCd. The Committee considered it was reasonable to assume daratumumab was associated with a small HRQOL benefit in global health status and slightly more of an effect for the fatigue score with D-VCd.

8.25. The Committee noted further evidence from ANDROMEDA including a publication of safety-run in results reported by Palladini et al. (Blood. 2020;136:71-80), conference presentation slides, oral presentations and abstracts that were submitted by the supplier.

8.26. Overall, the Committee considered that ANDROMEDA was a good quality study providing:

- strong evidence of benefit with deep, rapid haematological CR and VGPR for a substantial proportion of patients that was faster than the bortezomib-containing VCd (CyBorD) regimen alone, with an acceptable safety profile. The Committee considered these benefits were very relevant for fast and effective treatment of AL amyloidosis, although it was unclear how this benefit might translate to survival.

- evidence of improved organ responses at six months and prolonged organ deterioration PFS. The Committee considered that the indirect measures used

for cardiac and renal responses (rather than hard outcomes, eg decreased proteinuria rather than creatinine clearance) made it uncertain whether these organ responses translated into long-term organ function outcomes and considered it was unlikely that this would substantially change organ transplant rates.

8.27. The Committee noted that the use of daratumumab increased the number of patients with a VGPR in the ANDROMEDA study. Patients with CR or VGPR were associated with prolonged survival, although this remains poorly quantified in the literature (Muchtar et al. Mayo Clin Proc. 2019;94:472-83). Similarly, the Committee noted that patients with cardiac disease who had good NT-proBNP response had improved survival (Eckhert et al. Br J Haematol, 2019;186:144-6), however, there was limited evidence for OS or HRQOL benefits in the ANDROMEDA trial and follow-up review.

8.28. The Committee considered that the evidence from ANDROMEDA supported treatment of patients with cardiac stage IIIa and IIIb disease, with good benefit expected in stage IIIa, although only some patients with stage IIIb may benefit. The Committee considered it was reasonable for patients with stage IIIb disease to be able to trial daratumumab given some evidence of benefit in a disease with poor prognosis and considered that patients would likely discontinue after six months if the trial were unsuccessful.

8.29. The Committee was made aware of evidence based on cardiac response by NT-proBNP in patients with cardiac AL amyloidosis who received median two lines of therapy, which reported five-year survival of 96% in those who received a CR and 74% in those who received a VGPR (Eckhert et al. Br J Haematol, 2019;186:144-6). The Committee considered that there was a reasonable link between this endpoint as a measure of response and a survival benefit in this patient population. The Committee considered that there appeared to be a significant relationship between response to treatment and overall survival, with this relationship stronger for patients with AL amyloidosis than that observed in multiple myeloma. The Committee therefore considered that while there was no significant OS benefit offered by daratumumab after 15 months (from median 20.3 months follow-up data), it was reasonable to assume that daratumumab offered a survival benefit in this setting, and that this survival benefit may become apparent after 4 years.

8.30. The Committee considered that daratumumab IV could similarly be used to treat this population, noting that CaTSoP has previously considered there was no evidence to suggest a difference in efficacy between daratumumab IV and SC for multiple myeloma (CaTSoP, July 2021). The Committee considered that there was no evidence to indicate that the use of daratumumab IV would present a risk of volume overload in AL amyloidosis and that careful patient selection by clinicians and appropriate management would be reasonable for patient safety (eg. in cases with cardiac involvement). The Committee therefore considered it reasonable to also consider funding the IV formulation for AL amyloidosis, for use in appropriate cases as per clinician's judgement.

8.31. The Committee considered that resource use for patient identification and diagnosis would not be expected to change with funding of daratumumab for AL amyloidosis. The Committee considered that the SC formulation would be suitable for use in outpatient clinics, although noted that it has a shorter shelf life than bortezomib, a short expiry once reconstituted, and a large volume to administer which may present challenges for administration in the community as previously noted by CaTSoP in July 2021.

8.32. The Committee considered that daratumumab SC administered for the treatment of AL amyloidosis in primary care could result in administration-related reactions in up to 10% of patients, with most occurring at the first administration. The Committee considered that the management of complex reactions would be challenging in primary care. The Committee considered that the subsequent administration duration could be adjusted if appropriate for those who did not have a reaction.

8.33. The Committee considered that the use of daratumumab for the treatment of patients with newly diagnosed AL amyloidosis each year could reasonably be inferred from the number of patients receiving bortezomib via Special Authority, although acknowledged that the funding of a new agent for this patient group may increase this number to slightly above 30 patients per year. The Committee considered that uptake estimated at 100% was too high considering the use of bortezomib in most, but not all, cases.

8.34. The Committee considered that the Special Authority criteria for daratumumab for AL amyloidosis should include appropriate stopping criteria following a reasonable period of treatment in order to determine its effect. The Committee considered that six months may be too early for this assessment of benefit and therefore proposed 12 months. However, the Committee considered that Pharmac should seek advice from the Cancer Treatments Advisory Committee regarding appropriate stopping criteria that Pharmac could use, and their view of using a 12-month duration of approval.

8.35. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for daratumumab (IV or SC) if it were to be funded in New Zealand for AL amyloidosis. 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	Newly diagnosed systemic light chain (AL) amyloidosis
Intervention	D-VCd = daratumumab (IV or SC), bortezomib, cyclophosphamide and dexamethasone x 6 cycles followed by daratumumab (IV or SC) until disease progression/max 24 cycles. Daratumumab administered as follows: - Weeks 1-8 given weekly (8 doses) - Weeks 9-24 given every 2 weeks (8 doses) - Weeks 25 onwards given every 4 weeks until disease progression Median treatment duration of 38 weeks.
Comparator(s)	VCd = bortezomib, cyclophosphamide and dexamethasone x 6 cycles
Outcome(s)	• Improved haematological response rate • Improved major organ deterioration progression-free survival No direct evidence of survival benefit from ANDROMEDA; survival benefit is likely based on increased response rate and association between treatment response and overall survival • Quality of life – likely a small effect in short term for global health status and fatigue score with D-VCd; greater uncertainty about magnitude of long-term quality of life benefit ANDROMEDA found the percentage of daratumumab (D-VCd) treated patients who experienced haematological complete response, was 53% vs. 18% of VCd. The study also found a hazard ratio for major organ deterioration of 0.58 for D-VCd treated patients vs. VCd.
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 moderate to severe atopic dermatitis

Application

9.1. The Committee reviewed the application for upadacitinib for the treatment of moderate to severe atopic dermatitis.

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

Recommendation

9.3. The Committee recommended that upadacitinib for the treatment of moderate to severe atopic dermatitis be listed with a high priority subject to the following Special Authority criteria:

> **Initial application – (atopic dermatitis)** only from a relevant specialist.
> Approvals valid for 5 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has atopic dermatitis, defined by an Eczema Area and Severity Index score of ≥16 and a Physician's Global Assessment score of ≥3 at baseline; and
> 2. Patient must be over the age of 12; and
> 3. Patient must have received insufficient benefit or be contraindicated to topical therapies (including topical corticosteroids or topical calcineurin inhibitors), for a 28-day trial over a period within the last 6 months.
> **4.** Patient has trialled and received insufficient benefit from at least one systemic therapy (eg ciclosporin, azathioprine, methotrexate or mycophenolate mofetil) unless contraindicated
>
> **Renewal – (atopic dermatitis)** only from a relevant specialist.
> Approvals valid for 6 months for applications where the patient has achieved a 75% reduction in EASI score (EASI 75) or greater after 16 weeks of treatment.

9.4. In making this recommendation, the Committee considered the high health need and strong evidence of effectiveness of upadacitinib in this patient population.

9.5. The Committee considered that advice should be sought from the Dermatology Advisory Committee regarding:

- the potential for short courses of treatment due to upadacitinib's rapid onset of effect and likely usage patterns for upadacitinib
- the appropriateness of using upadacitinib for patients under the age of 12, especially considering the lack of data in this age group
- the inclusion of a Dermatology Life Quality Index (DLQI) score improvement within the proposed renewal criteria
- the current treatment sequence for patients with moderate to severe atopic dermatitis and the most appropriate placement of upadacitinib within this treatment sequence
- the appropriate prescriber type to support practical access for the intended population.

Discussion

Māori impact

9.6. The Committee noted that dermatitis disproportionately affects Māori and considered that access to specialist dermatology services is a significant barrier to receiving treatment. The Committee considered that this barrier would likely disproportionately affect Māori given socioeconomic factors for this population. The Committee also considered that Māori are more likely to live in areas of higher socioeconomic deprivation with lower grade housing, which may increase susceptibility to developing dermatitis. The Committee noted that that treatment of atopic dermatitis is not currently a Government health priority.

Discussion

9.7. The Committee noted that atopic dermatitis, or eczema, is a chronic, relapsing, pruritic, inflammatory skin disease which occurs more frequently in children than adults. The Committee noted that atopic dermatitis is a complex condition caused by a combination of genetic and environmental factors, and is characterised by cutaneous inflammation, immune dysregulation, and epidermal barrier dysfunction. The Committee noted that complications that arise from atopic dermatitis including a higher susceptibility to skin infections. The Committee noted that atopic dermatitis has a significant psychosocial and quality-of-life impact, causing emotional as well as physical distress.

9.8. The Committee noted a UK population-based study using GP data reporting on the prevalence of eczema (Lusignan et al. Clin Exp Allergy. 2021;51:471-82). The Committee noted that eczema had a bimodal distribution across the lifespan and that differences in the incidence and prevalence of eczema by ethnicity, geography, sex, and socio-economic status varied in magnitude throughout the life course. The Committee noted another prevalence study, based on Australian data, which indicated that the overall prevalence of eczema is 6.3%, which would equate to approximately 312,800 people in New Zealand in 2022 (Chidwick et al. Australian Journal of Dermatology. 2020;61:319-327). The Committee also noted that Chidwick et al. reported that 84.4% of individuals with atopic dermatitis are aged 12 and over, and that 21.4% of the population affected by eczema have moderate to severe eczema.

9.9. The Committee noted that the Dermatology Subcommittee reviewed an application for topical pimecrolimus for atopic dermatitis in October 2017 and stated that atopic dermatitis is a common disease affecting up to 20% of children and 5% of adults, with a prevalence of 15% and 16%, respectively, in Māori children and Pacific children. The Committee noted that environmental factors influence the occurrence of atopic dermatitis, and that living in damp and leaky homes is associated with development of atopic dermatitis.

9.10. The Committee noted that moderate to severe atopic dermatitis can be defined in multiple ways including, but not limited to, physical assessment of disease severity (physician's global assessment (PGA)), Eczema Area & Severity Index (EASI), Patient Oriented Eczema Measure (POEM), and quality-of-life measures such as Dermatology Life Quality Index (DLQI). The Committee noted that EASI is one of the most commonly used measures and consists of a simple scoring system to assess the extent and severity of eczema and noted that a score of upwards of 7.1 indicated moderate disease, and a score of 21.1 or more indicated severe disease. The Committee considered that a 75% decrease in EASI score (EASI75) correlates to a significant decrease in symptom burden and considered that this would be associated with a positive impact on patient quality of life.

9.11. The Committee noted that PGA is scored from 0 to 4, with a score of 3 indicating moderate, and 4 indicating severe disease. The Committee noted that POEM scoring has a maximum score of 28, and that a score of 8 to 16 indicates moderate eczema, and that 17 or above indicates severe disease. The Committee noted that DLQI is a 10-item questionnaire with a maximum score of 30; a score of ≥10 is considered severe; a change in score of 4 or more is considered the minimal clinically important change (MCID).

9.12. The Committee noted that moderate to severe atopic dermatitis is currently treated with emollients, topical corticosteroids, and for facial atopic dermatitis, topical calcineurin inhibitors such as pimecrolimus and tacrolimus. The Committee noted that patients who do not see a response with topical treatments are offered systemic immunosuppressant therapy with ciclosporin, as well as treatments that are not specifically approved for the treatment of atopic dermatitis, such as methotrexate, azathioprine, and mycophenolate mofetil. The Committee noted that phototherapy can also be beneficial to patients but noted that access to this is limited in Aotearoa New Zealand, and the evidence of benefit

is limited. The Committee noted that patients are likely to be referred to specialist secondary care if they require systemic therapy or standard flare management protocols are not providing adequate benefit.

9.13. The Committee noted that Australian Consensus Guidelines for the treatment of moderate to severe atopic dermatitis suggest systemic immunosuppressants be used secondarily to flare-management protocol, but do not specify the order in which respective immunosuppressants should be used if one, or more, are not tolerated or effective (Smith et al. Australas J Dermatol. 2020;61:23-32). The Committee also noted a review by Rademaker et al. which specified that systemic therapy should be an option for all patients with atopic dermatitis where their quality of life is impacted significantly, and that due to the high cost of newer emerging agents, any new agents are likely to remain second-line to conventional systemic therapies (Rademaker et al. Australas J Dermatol. 2020;61:9-22). The Committee noted that Rademaker et al stated in their review that "patients should have tried and failed, or be contraindicated, to conventional systemic therapies (at least two of phototherapy, ciclosporin, methotrexate, azathioprine or mycophenolate), over a period of at least 6 months, before considering one of the newer agents."

9.14. The Committee noted a published technology assessment by NICE in 2018 for the monoclonal antibody dupilumab for the treatment of moderate to severe atopic dermatitis. The Committee noted that dupilumab is recommended by NICE as an option for the treatment of moderate to severe atopic dermatitis if the disease has not responded to at least one other systemic therapy. The Committee noted that dupilumab is an IL4 inhibitor, which targets cytokine signalling via Th2 inhibition which initiates and maintains abnormal inflammatory pathways.

9.15. The Committee noted a review article from 2021 which outlines the variable pathophysiology of atopic dermatitis, as well as novel therapies, such as monoclonal antibodies and small molecules, which target different cellular and immunologic processes (Ahn et al. Ann Dermatol. 2021;33:1-10). The Committee noted janus kinase (JAK) inhibitors, a category of small molecules, are known to be well tolerated when used in the treatment of other inflammatory indications such as rheumatoid arthritis and inflammatory bowel diseases. The Committee noted that JAK inhibitors as a class have uncommon but potentially serious adverse effects, the most common of which are infections such as herpes zoster and tuberculosis. The Committee considered that a recombinant herpes zoster vaccine would be appropriate for patients on immunosuppressive treatments.

9.16. The Committee noted that upadacitinib is a reversible JAK1 selective inhibitor which is taken once daily at a dose of 15 or 30 mg for the treatment of atopic dermatitis. The Committee noted that the applicant's submission did not provide any publications of comparisons of upadacitinib against current standard of care with systemic therapies but provided an indirect comparison of dupilumab versus systemic therapy. The committee noted that upadacitinib is funded for the treatment of rheumatoid arthritis subject to a special authority.

9.17. The Committee noted that in the United States, there is a black box warning associated with upadacitinib that notes the occurrence of serious infections, lymphoma, and other malignancies that have been observed in patients treated with upadacitinib and that the warning also notes that thrombosis has occurred in patients treated with JAK inhibitors used to treat inflammatory conditions (not specific to upadacitinib). The Committee noted that upadacitinib had Medsafe approval for the treatment of atopic dermatitis.

9.18. The Committee noted a systematic review and network meta-analysis comparing the effectiveness and safety of systemic immunomodulatory treatments for patients with atopic dermatitis (Drucker et al. JAMA Dermatol. 2020;156:659-67). The Committee noted that upadacitinib 15mg and 30mg daily, but not 7.5 mg, was associated with a clinically meaningful improvement in POEM score compared with placebo. The

Committee also noted that treatment with dupilumab was associated with improvement in the EASI score versus placebo (mean difference 11.3-point reduction; 95% credible interval 9.7-13.1). The Committee noted that cyclosporin and dupilumab were similarly effective versus placebo in clearing clinical signs of atopic dermatitis and may be superior to methotrexate (standardized mean difference, −0.6; 95% credible interval −1.1 to 0.0) and azathioprine (standardized mean difference, −0.4; 95% credible interval, −0.8 to −0.1). The Committee noted that all treatments listed were more effective than placebo in managing atopic dermatitis. The Committee noted that most studies included in the Drucker et al. analysis and review were of 16-week duration and considered that there was a lack of studies directly comparing established and novel treatments beyond 16 weeks.

9.19. The Committee noted the pivotal evidence for upadacitinib in the treatment of atopic dermatitis:

9.19.1. Reich et al. Lancet. 2021;397:2169-81: the AD-UP phase III, randomised, placebo controlled, double blind, multicentre trial of adults and adolescents with chronic atopic dermatitis that was moderate to severe who were treated with either upadacitinib 15 mg or 30 mg once daily in combination with topical corticosteroids, or placebo once daily with topical corticosteroids, for 16 weeks followed by a 120-week blinded extension. The co-primary endpoints were validated Investigator's Global Assessment for atopic dermatitis (vIGA-AD) response (defined as a vIGA-AD score of 0/1 [almost clear] with ≥2 grades of reduction from baseline) and at least 75% reduction in Eczema Area and Severity Index score (EASI-75) at week 16. The Committee noted that both primary endpoints were met quickly, and considered that the patient population was representative of the New Zealand population with atopic dermatitis.

9.19.2. Guttman-Yassky et al. J Allergy Clin Immunol. 2020;145:877-84: the M16-048 phase 2b multicentre, randomized, placebo-controlled, double-blind dose-ranging study of patients aged 18-75 years with confirmed atopic dermatitis for whom topical corticosteroids are inadequate or contraindicated who received upadacitinib (7.5mg, 15mg, or 30mg once daily) or placebo (once daily) for 16 weeks.

9.19.3. Guttman-Yassky et al. Lancet. 2021;397:2151-68: the MEASURE-UP 1 and 2 replicate phase III randomised, double-blind, placebo controlled, multicentre trials of adolescents and adults with moderate-to-severe atopic dermatitis who were given upadacitinib 15 mg or 30 mg once daily, or placebo once daily for 16 weeks. The primary endpoints for the study were EASI 75 and a vIGA-AD score of 0/1 with at least 2 grades of reduction from baseline. Both primary endpoints were met in both studies at week 16. The Committee considered that the patients enrolled in this trial were representative of the New Zealand patient population in terms of their severity of disease. The Committee noted that approximately half of the participants in the trial had received prior systemic therapy. The Committee also noted that there were no new safety signals reported that have not been previously identified from other indications, which were primarily increased incidence of herpes zoster and acne.

9.19.4. The unpublished RISING-UP phase III, randomised, double-blind, placebo controlled, multicentre trial of those aged 12-75 years with active moderate to severe atopic dermatitis who are able to tolerate topical corticosteroids who received upadacitinib (15 mg or 30 mg) once daily in combination with topical steroid use, or placebo in combination with topical corticosteroid use for 16 weeks, followed by a blinded extension to week 52 where subjects on placebo were re-randomised to receive 15 mg or 30 mg upadacitinib.

9.20. The Committee also noted the following evidence relating to the use of upadacitinib in the treatment of atopic dermatitis:

9.20.1. Kerschbaumer et al. RMD Open. 2020;6:e001374

9.20.2. Naubaum et al. J Dermatolog Tret. 2020;online ahead of print

9.20.3. Silverberg et al. J Eur Dermatol Venereol. 2021;35:1797-1810

9.20.4. Siegels et al. Allergy. 2021;76:1053-76

9.21. The Committee noted the HEADS-UP head-to-head, phase IIIb, multicentre, randomized, double-blinded, double-dummy, active-controlled clinical trial comparing the safety and efficacy of upadacitinib with dupilumab among 692 adults with moderate to severe atopic dermatitis who were candidates for systemic therapy randomised to receive oral upadacitinib, 30 mg once daily, or subcutaneous dupilumab, 300 mg every second week (Blauvelt et al. JAMA Dermatol. 2021;157:1047-55). The Committee noted that rescue therapy, defined as any topical or systemic immunomodulatory treatment initiated for atopic dermatitis, could be given at any time per investigator discretion and that patients who received rescue therapy were considered non-responders for binary end points after the initiation of rescue therapy. The Committee noted that the primary outcome of the trial was EASI75 and that at week 16, 247 patients receiving upadacitinib (71.0%) and 210 patients receiving dupilumab (61.1%) achieved EASI75 (P = 0.006). The Committee noted that patients receiving upadacitinib also had a significantly reduced itch score compared to those taking dupilumab. The Committee noted that the patient characteristics were similar to those reported in the above upadacitinib trials, but that previous systemic therapy was not reported. The Committee noted that the adverse events reported in the study were consistent with the known safety profiles of each drug.

9.22. The Committee noted a systematic review and network meta-analysis on the short-term efficacy and safety of biologics and small molecule drugs for the treatment of moderate to severe atopic dermatitis (Pereyra-Rodriguez et al. Life (Basel). 2021;11:927). The Committee noted that upadacitinib was rated highly in achieving EASI75 both as monotherapy and in combination with topical corticosteroids, but that the drugs with the highest probability of presenting adverse effects were the Janus kinase (JAK) inhibitors, upadacitinib and abrocitinib in monotherapy and baricitinib in combination with topical corticosteroids.

9.23. The Committee considered that the strength and quality of evidence for upadacitinib in the treatment of atopic dermatitis is good but noted that there is no evidence for treatment in those under the age of 12, and that there is currently no Medsafe approval for upadacitinib for this age group. The Committee considered a recommendation regarding use in patients under the age of 12 years required further consideration and evidence regarding the efficacy and safety profile in this age group. The Committee considered the Dermatology Advisory Committee would be best placed to consider treatment for patients under the age of 12 years

9.24. The Committee noted that atopic dermatitis is a disease of “flare-ups”, and that ideal treatment should work quickly to subdue itching and inflammation, as well as have a long-term maintenance effect. The Committee considered that upadacitinib shows evidence of fast action and a sustained reduction in symptom burden.

9.25. The Committee considered that if upadacitinib were to be funded, patients would likely continue to use topical corticosteroids/calcineurin inhibitors where needed (such as during flare-ups associated with changing seasons), as well as emollient and barrier creams.

9.26. The Committee noted that dermatitis disproportionately affects Māori and Pacific people; for those aged 13-14 years, the prevalence of atopic dermatitis for Māori was 2.1%, compared to 0.8% for Europeans and 2.8% for Pacific people (Clayton et al. Asia Pac Allergy. 2013;3:161-78). The Committee noted that access to specialist dermatology services is a significant barrier to receiving treatment and considered that this barrier would likely disproportionately affect Māori and Pacific peoples given socioeconomic factors for these populations. The Committee considered that upadacitinib would need

to be initiated in secondary care (specialist dermatology services) given the requirement to have tried at least one other systemic therapy initiated in secondary care recognising the difficulties in equity of access to treatment this might cause. The Committee considered that advice should be sought from the Dermatology Subcommittee on the best placement of upadacitinib in the treatment sequence and the prescriber restrictions which would support practical access to upadacitinib for the intended population.

9.27. The Committee considered that adherence to treatment is likely to be high in patients due to rapid effect of upadacitinib but considered that patients may stop taking treatment once their atopic dermatitis is controlled and their symptom burden is low. The Committee considered that, as atopic dermatitis is relapsing in nature, that patients may stop and start treatment depending on flare-ups and control of symptoms between flare ups. The Committee considered that advice should be sought from the Dermatology Subcommittee regarding the appropriateness of short treatment duration in accordance with flares. The Committee considered that there is limited long-term evidence for upadacitinib, and that it is unclear how long upadacitinib would have an effect after treatment is stopped.

9.28. The Committee considered that acne as a side effect of upadacitinib would not be a reason for most patients to discontinue use of upadacitinib. The Committee noted that currently available JAK inhibitors seem to have slightly different effects, and so long-term safety and efficacy for upadacitinib should not be extrapolated based on the other agents. The Committee noted that some longer-term safety data is available from the use of upadacitinib in rheumatoid arthritis. The Committee also considered that it is unclear if there would be a bypass mechanism for upadacitinib but noted that there is no data to suggest that there may be development of resistance over time.

9.29. The Committee considered that if upadacitinib were funded, hospitalisations and GP visits due to atopic dermatitis may decrease which would lead to health sector savings. The Committee considered, however, that the majority of hospitalisations occur in children under the age of five and are related to secondary infections, and that these patients may not be eligible for upadacitinib. The Committee also considered it was not appropriate to extrapolate a reduction in hospitalisations from overseas (such as in the UK) given the lower rates of dermatology related hospitalisations in New Zealand and limited availability of dermatologists. Therefore, the Committee considered that hospitalisation rates may not be an appropriate metric in cost analysis. The Committee considered that EASI75 relates to significant quality of life improvements for patients, and that this is an appropriate measure of improvement for patients with atopic dermatitis.

9.30. The committee considered the utility values used in Zimmerman et al. Journal of Drugs in Dermatology. 2018;17:7. to be appropriate for use in economic analysis, and noted that these values are similar to those used in other papers.

9.31. The Committee considered that the 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 moderate to severe 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 (AD): • AD is considered moderate to severe if the patient has an EASI score of 16 or higher and a PGA score of 3 or higher at baseline • Patient must have tried and failed or be contraindicated to topical therapies (including TCS OR TCI), for a 28-day trial over a period within the last 6 months, and at least 1 systemic agent (methotrexate, ciclosporin, etc)
Intervention	15 mg or 30 mg upadacitinib taken once daily. The submission assumes that 67% of patients who initiate treatment would take the 15mg dose, while the remaining 33% would take the 30mg dose. No maximum treatment duration. Treatment would be renewed if the patient achieves an EASI 75 response after 16 weeks of treatment
Comparator(s)	Best supportive care in the form of optimal skin care (soap-free wash, luke-warm bathing, emollients) with or without the concomitant use of topical corticosteroids and a systemic agent.
Outcome(s)	• Improved quality of life by reducing the severity of atopic dermatitis, as measured by greater rates of patients achieving EASI 75 response. Reduced hospitalisations may be associated with improved EASI 75 responses; however this reduction is likely to be small given that the majority of AD hospitalisations are patients under age five.
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. Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) in the treatment of cystic fibrosis patients aged 6 years and older with at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene

Application

10.1. The Committee reviewed the application for elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) in the treatment of cystic fibrosis (CF) patients aged 6 years and older with at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

10.2. The Committee noted that Pharmac sought advice from the Committee regarding elexacaftor/tezacaftor/ivacaftor for the treatment of people with cystic fibrosis aged 6 years and older in the context of:

10.2.1. a supplier submission received July 2021 from Vertex Pharmaceuticals

10.2.2. correspondence and supporting evidence from Cystic Fibrosis New Zealand

10.2.3. information provided by treaters of cystic fibrosis from Pharmac's former Cystic Fibrosis Panel (disestablished 1 December 2020) to Pharmac in August 2021

10.2.4. the recommendations and considerations from the Respiratory Subcommittee (meeting held 26 August 2021) regarding this application.

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** 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, subject to the following Special Authority criteria:

Initial application
Applications only from a respiratory specialist. Approvals valid for patients that meet the following criteria:

1. Patient has been diagnosed with cystic fibrosis; and
2. Patient is 12 years of age or older; and
3. Patient must have a F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene on at least 1 allele; and
4. Patient has a sweat chloride value of at least 60 mmol/L by quantitative pilocarpine iontophoresis or by Macroduct sweat collection system; 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

Advice to be sought from the Respiratory Advisory Committee regarding the inclusion of renewal criteria and stopping criteria.

10.5. The Committee **recommended** that ELX/TEZ/IVA for the treatment of CF patients aged less than 12 years of age who have at least one F508del mutation in the CF transmembrane conductance regulator (CFTR) gene be **deferred** pending the availability of further data supporting the evidence of efficacy of ELX/TEZ/IVA for patients less than 12 years of age.

10.6. The Committee **recommended** that ELX/TEZ/IVA for the treatment of CF patients for the wide range of mutations with *in vitro* data supporting responsiveness to ELX/TEZ/IVA (Eligible mutations are listed on table 5 of FDA highlights of prescribing information June 2021 and www.cftr2.org) be **deferred** pending *in vivo* efficacy data supporting the efficacy of ELX/TEZ/IVA for patients with these mutations in the CFTR gene.

10.7. In making these recommendations the Committee considered:

10.7.1. The high health need of this population and the apparent rapid benefit of ELX/TEZ/IVA for CF patients, however considered that there is a lack of longer-term evidence of benefit in this patient group.

10.7.2. The insufficient evidence supporting the efficacy of ELX/TEZ/IVA for CF patients less than 12 years of age or in patients with mutations responsive *in vitro* to ELX/TEZ/IVA.

10.7.3. The substantial cost of this treatment for this patient group and the impact that funding this treatment may have on the Combined Pharmaceutical Budget.

10.8. The Committee also noted that there is a structural inequity in CF testing at the genotype level and considered that it may be necessary to investigate additional resourcing to identify disease genotypes in Māori and Pacific people to ensure eligibility and improve equity for these patients.

10.9. The Committee considered that further advice should be sought from the Respiratory Advisory Committee regarding:

10.9.1. whether a phenotypic definition of CF may be a more appropriate than genotypic criteria for access

10.9.2. appropriate stopping criteria for the Special Authority if a phenotypic definition were appropriate to include, noting the difficulty in establishing a true baseline from which to compare against.

Discussion

Māori impact

10.10. The Committee noted that there is a structural inequity in the investigation of new treatments for cystic fibrosis and testing at the genotype level and considered that it may be necessary to investigate additional resourcing to identify disease genotypes in Māori to ensure eligibility and improve equity for these patients. The Committee noted that there is insufficient evidence relating to Māori patients with cystic fibrosis to determine if they are overrepresented or have worse outcomes than the non-Māori cystic fibrosis patient population. However, the Committee noted the Respiratory Subcommittee consideration that it was likely that Māori with cystic fibrosis would experience worse outcomes than non-Māori. Treatment of cystic fibrosis falls under the Government health priority of child wellbeing, as well being a chronic respiratory disease, which is one of the Government Health Priority conditions. Respiratory health is Māori health area of focus identified in Te Whaioranga.

Discussion

10.11. The Committee noted that the Respiratory Subcommittee reviewed the application for ELX/TEZ/IVA for the treatment for CF at its August 2021 meeting, where it was recommended for funding with a high priority. The Committee noted that the Respiratory Subcommittee recommended access for patients greater than 6 years of age for a wide range of patients to align with FDA eligible mutations (listed on table 5 of FDA highlights of prescribing information June 2021) and considered that this criteria included eligibility for patients with mutations for which benefit is not currently supported by evidence of benefit in patients.

10.12. The Committee noted that cystic fibrosis (CF) is a rare, genetic and progressive disease which causes multisystem organ impairment and premature death as a result of a defective CFTR protein. This defective CFTR protein results in defective transport of chloride and other ions across the surface of epithelial cells and causes a disruption in fluid homeostasis. The Committee noted that this leads to the production and retention of thick secretions in multiple organ systems and that this build-up of secretions has serious clinical consequences for multiple organs including the lungs, pancreas, liver, intestine, and reproductive system. The Committee also noted that psychological problems for patients also arise, due to the high associated symptom and treatment burden, and living with a terminal illness from a young age.

10.13. The Committee noted that advances in best supportive care over the last decade have improved life expectancy for patients with CF by 10-15 years, and that the current life expectancy of patients with CF in New Zealand is approximately 35-45 years. The Committee noted that CF is a disease with a variable rate of progression over time, but that the health need for patients may increase as they age due to accumulating symptom and treatment burden and associated lung and organ dysfunction over time.

10.14. The Committee noted that patients' day-to-day symptom burden is high and includes cough and high production of sputum, frequent infections, loss of lung function over time, as well as having to regularly take time off school or work, and that some patients are restricted to part time education or work as a result. The Committee also noted that caregivers of CF patients also regularly must take time off work to support their dependents. The Committee also noted that the daily treatment burden of CF is high and increases with age and disease severity and that daily treatment can include three to four hours of nebulised treatments, in addition to regular clinical visits with specialists, regular hospitalisations, and having to take multiple other medications daily. The Committee also noted that the CF Registry (maintained by Cystic Fibrosis New Zealand) contains substantial information on patient level outcomes from CF (Port CF Data Registry, 2017 Registry Report, Cystic Fibrosis NZ). The Committee considered that it would be useful to obtain the relevant clinical considerations for patients with CF in New Zealand from the CF registry.

10.15. The Committee noted that the New Zealand Cystic Fibrosis Registry from 2017 cites that there are 498 CF patients in New Zealand but that this excludes those who have undergone lung transplant. The Committee also noted that the Respiratory Subcommittee referenced a prevalence of 540 patients with CF in New Zealand and noted that it was unclear how this population estimate was provided. The Committee noted that due to the way in which the data is presented in the CF Registry reports it is difficult to extrapolate exactly how many children aged 6 and under have CF in New Zealand, however the Committee, based on the CF registry data, estimated approximately 390 patients would be over the age of 7 and would expect a slightly larger patient number for those over 6 years.

10.16. The Committee noted further information from the CF Registry outlining further health needs of patients and their whānau, including that over half of CF patients are infected with Staphylococcus aureus, approximately a third of adults with CF and approximately 11% of children with CF have CF related diabetes

10.17. The Committee noted that CF can be caused by various mutations which can be grouped into classes (protein production, protein processing, gating, conduction, and insufficient protein), which pertain to specific defects, but which sometimes overlap. The Committee noted that diagnostic assays for CF and the reporting of CFTR variant frequencies are optimised for European populations and may contribute to underrepresentation of CF incidence and prevalence worldwide in non-European populations, for example that the F508del mutation is absent from populations with predominantly East Asian ancestry though CF is still prevalent in these populations (Bell et al. Lancet Respir Med. 2020;8:65-124). The Committee considered that variations in genotype by ethnicity in New Zealand are unknown at this time.

10.18. The Committee noted that there is insufficient evidence relating to Māori and Pacific patients with CF to determine if they are overrepresented or have worse outcomes than the non-Māori CF patient population. The Committee noted a study by McGarry et al. which found that patients with CF from minority groups are less likely to have mutations what would make them eligible for CFTR modulator treatment (McGarry et al. Pediatr Pulmonol. 2021;56:1496-1503). The Committee also noted that McGarry et al. reported that the FEV1 percentage for minority groups who were not eligible for CFTR modulators was similar to that of non-Hispanic white patients who were eligible for CFTR modulators and considered that this could indicate that genotypes ineligible for CFTR modulators may have similar disease phenotypes. The Committee noted that there is a concern regarding certain mutations not consistently representing a phenotype.

10.19. The Committee noted that there are a number of therapeutics in development for CF, including CFTR modulator therapies, therapies for mucociliary clearance, anti-inflammatory treatments, anti-infectives, gene therapies, and nutritional support. The Committee noted that there seems to be a shift in CF therapeutics development from highly specific targets to more generalised off-target CFTR effects.

10.20. The Committee noted that ELX/TEZ/IVA is a CFTR modulator which binds to different sites on normal and F508del-CFTR proteins to increase processing and trafficking to the epithelial cell surface, as well as potentiating the functioning of CTFR protein by increasing channel gating and enhancing chloride transport.

10.21. The Committee noted the following published trials relating to the use of ELX/TEZ/IVA in the treatment of CF in patients with at least one F508del mutation:

10.21.1. Study 102 (Middleton et al. N Engl J Med. 2019;381:1809-19, Jain et al. Pediatr Pulmonol. 2019;54:346-47 [conference abstract], Fajac et al. Thorax. 2021;76:A40-1 [conference abstract]): a phase III randomised, double-blind, active-controlled, parallel-group study that included 405 stable CF patients aged 12 years and older with ppFEV1 between 40% and 90% and who were heterozygous for the F508del in the CFTR gene with a MF mutation (F/MF

patients). Patients were treated with either with ELX/TEZ/IVA (n=201) or placebo (n=204) over 24 weeks. At week 24, the mean absolute change in ppFEV1 between the two treatment groups from baseline was 14.3 (95% CI 12.7 to 15.8; p<0.001), and the mean absolute change in sweat chloride between the two treatment groups from baseline was -41.8 mmol/L (95% CI -44.4 to -39.3; p<0.001). Pulmonary exacerbations decreased by 63% in the ELX/TEZ/IVA treated group (rate ratio 0.37; 95% CI 0.25 to 0.55; p<0.001) and CFQ-R Respiratory Domain score increased by 20 points (least squares mean difference 20.2 between ELX/TEZ/IVA and placebo; 95% CI 17.5 to 23.0; p<0.001).

10.21.2. Study 103 (Heijerman et al. Lancet. 2019;394:1940-48): a phase III randomised, double-blind, active-controlled, parallel-group study that included 113 stable CF patients aged 12 years and older homozygous for F508del-CFTR mutation (F/F patients) with ppFEV1 between 40% and 90%. Patients were treated with either ELX/TEZ/IVA (n=56) or TEZ/IVA (n=52) over 4 weeks. At week 4, the mean absolute change in ppFEV1 between the two treatment groups from baseline was 10.0 (95% CI 7.4 to 12.6; p<0.0001) and the mean absolute change in sweat chloride between the two treatment groups from baseline was -45.1 mmol/L (95% CI -50.1 to -40.1; p<0.0001). CFQ-R Respiratory Domain score increased by 16.0 points in the ELX/TEZ/IVA treated group versus a decrease of 1.4 in the TEZ/IVA group (mean difference 17.4 between ELX/TEZ/IVA and TEZ/IVA; 95% CI 11.8 to 23.0; p<0.0001). In Study 103, the health-related quality of life improvements with ELX/TEZ/IVA over TEZ/IVA were seen in 7 of the 11 CFQ-R non-RD scores, including vitality, physical functioning, and health perceptions.

10.21.3. Study 104 (Barry et al. N Engl J Med. 2021;385:815-25), a phase III double-blind, randomised, active-controlled trial involving 258 CF patients aged 12 years or older who are heterozygous for F508del and a gating or residual function mutation (F/G and F/RF genotypes) treated with either ELX/TEZ/IVA (n=132) or active control (either IVA or TEZ/IVA n=126) for 8 weeks. Patients treated with ELZ/TEZ/IVA had a ppFEV1 mean absolute change from baseline of 3.7 (95% CI 2.8 to 4.6) compared with 0.2 in the active control group (95% CI -0.7 to 1.1; between group difference 3.5; 95% CI 2.2 to 4.7; p<0.001). The sweat chloride concentration had a mean change from baseline of -22.3 mmol/L in the ELZ/TEZ/IVA treated group (95% CI -24.5 to -20.2) compared with 0.7 mmol/L in the active control group (95% CI -1.4 to 2.8; between-group difference -23.1 mmol/L; 95% CI -26.1 to -20.1; p<0.001). The ELX/TEZ/IVA treated group achieved a mean difference of 10.3 in CFQ-R respiratory domain score (95% CI 8.0 to 12.7) compared with 1.6 in the active control group (95% CI -0.8 to 4.1; between-group difference 8.7; 95% CI 5.3 to 12.1). Subgroup analyses of patients with F/G and F/RF genotypes were consistent with the results of the primary overall group analysis.

10.21.4. Study 106 (Zemanick et al. Am J Respir Crit Care Med. 2021;203:1522-32): a phase III 24-week open-label study that included 66 stable CF patients aged 6 to 11 years homozygous for F508del (F/F genotype) or heterozygous for F508del and an MF mutation that is not responsive to IVA and TEZ/IVA (F/MF genotype). Patients were treated with ELX/TEZ/IVA for 24 weeks. F/F patients had a mean absolute change from baseline in ppFEV1 of 12.2 (95% CI 7.2 to 15.2; p<0.0001), a mean absolute change in sweat chloride of -70.4 mmol/L (95% CI -75.6 to -63.3; p<0.0001), a mean absolute change from baseline in CFQ-R Respiratory Domain Score of 7.0 points (95% CI 3.9 to 10.1), and a mean absolute change from baseline in lung clearance index (LCI2.5) of -1.64 (95% CI -2.34 to -0.94). Patients with F/MF mutations had mean absolute change from baseline in ppFEV1 of 9.1 (95% CI 7.2 to 15.2; p<0.0001), a mean absolute change in sweat chloride of -55.1 mmol/L (95% CI -59.0 to -51.2; p<0.0001), a mean absolute change from baseline in CFQ-R Respiratory Domain Score of 6.9 points (95% CI 3.2 to 10.6; p=0.0005), and a mean absolute change from baseline in LCI2.5 of 1.72 (95% CI -2.11, -1.33; p<0.0001). Overall, in Study 106 the mean absolute change from baseline in ppFEV1 for all

patients was 10.2 (95% CI 7.9 to 12.6; p<0.0001), the mean absolute change in sweat chloride from baseline was -60.9 mmol/L (95% CI -63.7, -58.2; p<0.0001), the mean absolute change from baseline in CFQ-R Respiratory Domain Score was 7.0 points (95% CI 4.7 to 9.2; p<0.0001), and the mean absolute change from baseline in LCI2.5 was -1.71 (95% CI -2.11 to -1.33; p<0.0001).

10.22. The Committee also noted the following studies relating to the use of ELX/TEZ/IVA in the treatment of CF:

10.22.1. Study 105 (unpublished, ClinicalTrials.gov Identifier: NCT03525574): 96-week results from patients enrolled in studies 102 and 103, where all patients were treated with ELX/TEZ/IVA.

10.22.2. Study 116 (unpublished, ClinicalTrials.gov Identifier: NCT04353817): a phase III randomised, double-blind, active-controlled, parallel-group study that included 121 stable CF patients aged 6 to 11 years who were heterozygous for F508del in the CFTR gene with a MF mutation (F/MF patients) treated with ELX/TEZ/IVA or placebo over 24 weeks.

10.22.3. Study 107 (ClinicalTrials.gov Identifier: NCT04183790): a roll-over study from Study 106 investigating the long-term safety, tolerability, efficacy, and pharmacodynamics of ELX/TEZ/IVA in patients with CF aged between 6 and 11 years.

10.23. The Committee noted that there is no long-term published data available past 24-weeks in patients over the age of 12, and that there is no published data for the use of ELX/TEZ/IVA in those under the age of 6 years. The Committee considered the strength and quality of evidence to be good overall but noted the lack of longer-term evidence and the variation between trial designs, specifically with regard to eligibility criteria and treatment run-in periods. The Committee considered that ppFEV1 is an important clinical outcome for these patients but that it does not comprehensively inform on a patient's overall lung function, and that 4-week studies are too short in duration to accurately measure any change. The Committee noted that there were few patients who discontinued ELX/TEZ/IVA due to adverse events, and that reported adherence rates were high for ELX/TEZ/IVA.

10.24. The Committee noted that the only currently available CFTR modulator in New Zealand is ivacaftor, which is available for less than 10% of the New Zealand CF population as it targets a specific subset of mutations. The Committee noted that the comparator treatment to ELX/TEZ/IVA for the majority of the New Zealand CF patient population is best supportive care. The Committee noted that approximately 87% of the current CF patient population have at least one F508del mutation (Port CF Data Registry, 2017 Registry Report, Cystic Fibrosis NZ) and would be eligible for ELX/TE/IVA if it were to be funded in New Zealand, without accounting for age as an eligibility criterion. The Committee noted that funding of ELX/TEZ/IVA would expand the patient population eligible for CFTR modulator treatment.

10.25. The Committee considered that the risks and benefits of treating those aged 6-11 years or 12 years and over would be similar in that treatment would be expected to alter the baseline progression of disease for all age groups. The Committee noted, however, that those aged 12 years or over are more likely to be symptomatic at the time of treatment initiation, and will thus have a more measurable improvement, whereas those aged 6-11 years will have a less measurable improvement having not yet experienced significant disease progression in line with the considerations of the Respiratory Subcommittee. The Committee noted that there is insufficient data on the use of ELX/TEZ/IVA in CF patient aged under 6 years but considered that treating this younger age group with CFTR modulators may prevent or delay disease worsening over time, which may prevent or delay the development of CF related comorbidities such as pancreatic insufficiency or malabsorption.

10.26. There Committee considered that there is significant uncertainty around the efficacy of ELX/TEZ/IVA for some genotypes and classes of mutations. The Committee noted that while the pivotal trials were open to a large and variable panel of mutations, there is no information on which mutations were actually present in those enrolled in the studies and noted that not all mutations could have been represented as there were more eligible mutations listed in the trial protocol than there were participants in the trials themselves. The Committee considered that it is likely that there are common phenotypes within mutation classes as opposed to mutation specific phenotypes.

10.27. The Committee noted that the Special Authority criteria suggested by the Respiratory Subcommittee for ELX/TEZ/IVA included all mutations listed in Table 5 of the FDA highlights of prescribing information June 2021, which includes mutations for which there is only *in vitro* evidence of effect and which requires extrapolation for efficacy *in vivo.* The Committee noted that this seems to be a normal practice in CF treatment research, but also noted that there is active debate in the literature as to whether all *in vitro* benefits translate into *in vivo* benefit in CFTR mutations. The Committee noted that the Respiratory Subcommittee also recommended funding for patients with cystic fibrosis-causing genes, including F508del, G551D and other mutations listed as cystic-fibrosis causing at www.cftr2.org. The Committee noted that the FDA is allowing access to patients with mutations which have had an *in vitro* response to ELX/TEZ/IVA, but that European agencies are less permissive only allowing access to those who have mutations with a proven *in vivo* benefit. The Committee noted that while there is a common effect within a class of mutations, it is possible that approximately 20% of European CF patients may not be eligible for CFTR modulator therapy due to unproven benefits in rare mutations, and that approximately 10% of all patients with a CF phenotype may not have any CFTR to modulate at all Fajac I. Sermet I. Cells. 2021;10:2793).

10.28. The Committee considered that advice should be sought from the Respiratory Advisory Committee regarding whether a phenotypic definition of CF may be a more appropriate than genotypic criteria for access, given the desire to achieve equity within the context of potentially inequitable testing and the concerns regarding the extrapolation of benefit from response of certain mutations to ELX/TEZ/IVA in vitro.

10.29. The Committee noted that quality of life in the ELX/TEZ/IVA pivotal studies was measured using CFQ-R respiratory domain scores. The Committee noted that the minimally clinically important difference (MCID) in CFQ-R score on treatment compared to baseline is approximately 8-10 points for exacerbations and approximately 4 points in a stable state (Quittner et al. Chest. 2009;135:1610-18). The Committee noted that all studies reported a CFQ-R respiratory domain score above the MCID and considered these scores to be clinically meaningful. The Committee considered, based on the clinically meaningful improvement in CFQ-R, the health utility of patients taking ELX/TEZ/IVA would similarly improve.

10.30. The Committee considered it reasonable to assume (in line with the Respiratory Subcommittee) that there would be a reduction in the number of pulmonary exacerbations in the 6–11-year-old age group after receiving ELX/TEZ/IVA. The Committee noted that patients under the age of 6 are unlikely to be symptomatic and considered that treatment with ELX/TEZ/IVA may not coincide as directly with a reduction in exacerbations. The Committee considered that while longer term data is expected for all age groups for whom funding has been requested, at this time, there is insufficient data to assess long-term outcomes from treatment with ELX/TEZ/IVA. The Committee considered ppFEV1 to not be an evidenced surrogate for ongoing exacerbations from the published trial data, in that Study 102 provided the only published data to support a reduction in exacerbations. The Committee considered that this would become known with longer follow up data from the other clinical trials.

10.31. The Committee noted an indirect treatment comparison conducted by the supplier which compared the efficacy of ELX/TEZ/IVA over 24-weeks to other relevant treatment

options in patients with F508del homozygous or heterozygous mutations. The Committee noted that all of the studies had run in periods and differences in baseline measurements such as ppFEV1. The Committee noted that the indirect treatment comparison used data from Study 109 (ClinicalTrials.gov Identifier: NCT04105972), which has not yet been published, and considered that this put the validity of the indirect comparison to question, as it is not clear if the patient population in study 109 is an appropriate representation of the F508del homozygous population.

10.32. The Committee considered that there was uncertainty around the long-term consequences of using CFTR modulator therapies, and if CF patients will in fact experience near-normal lifespans. The Committee considered that it was unknown if incidence of CF-related comorbidities such CF-related diabetes or infertility would decrease. The Committee considered that there are no non-clinical features of the ELX/TEZ/IVA tablet that may impact on use, either by the patient, by family, or by healthcare workers, but noted that liquid formulations may need to be available if data emerges for efficacy in patients under the age of 6 years.

10.33. The Committee considered that it was unclear if medical service costs for CF patients would change if patients were receiving ELX/TEZ/IVA compared to best supportive care. The Committee considered that there was uncertainty regarding the magnitude of impact on the healthcare utilisation if ELX/TEZ/IVA funded and that this would be driven by extrapolation and uncertain assumptions. The Committee considered that the modelling put forth by the Institute for Clinical and Economic Review (ICER) to reasonably reflect the health benefit of ELX/TEZ/IVA over time (Tice et al. Modulator Treatments for Cystic Fibrosis: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review, April 27, 2020).

10.34. The Committee considered that overall, ELX/TEZ/IVA has strong biological plausibility for efficacy and very promising short-term data. However, the Committee also considered that the available data is very limited, and that there is not enough information available to extrapolate the magnitude of long-term benefit.

10.35. The Committee noted that there may need to be an effective way of managing access for these patients and that a permissive Special Authority criterion may not effectively target treatment to those patients for whom a benefit would be expected. The Committee considered that it would be useful to seek further advice from the Respiratory Advisory Committee regarding the inclusion of renewal criteria that would effectively manage the uncertainty that exists in the data (eg reduction in exacerbations from baseline), in order to confirm benefit, and to consider whether a phenotypic criteria rather than one based on genotypes would enable more equitable access for this patient group. The Committee considered that it would be useful to investigate whether or not such access criteria exist in other jurisdictions.

10.36. The Committee noted that the cost of ELX/TEZ/IVA was substantial and would impact the ability to fund other medicines from the Combined Pharmaceutical Budget. The Committee considered that this was an important factor in the context of the lack of long term follow up data that exists.

10.37. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for ELX/TEZ/IVA if it were to be funded in New Zealand for the treatment of CF in patients over the age of 12 with at least one F508del mutation. 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	Cystic fibrosis patients 12 years and over with at least one F508del (F) mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. • F/F • F/MF • F/RF • F/G • F/R117H • F/not yet characterised
Intervention	ELX/TEZ/IVA • Patients <30kg one tablet in the morning containing 50mg (ELX), 25mg (TEZ), 37.5mg (IVA) and one tablet in the evening containing 75mg (IVA). • Patients >30kg one tablet in the morning containing 100mg (ELX), 50mg (TEZ), 75mg (IVA) and one tablet in the evening containing 150mg (IVA).
Comparator(s)	Patients with at least one F mutation - BSC Patients with at least one F mutation and one gating mutation (F/G) – Ivacaftor + BSC
Outcome(s)	• Lung function (in terms of ppFEV) • Weight-for-age z-score. • Reduced pulmonary exacerbation (PEx) rates. • Reduction in long term decline in ppFEV. • Improved quality of life. • Health sector savings (lung transplants and inpatient costs). • Improved survival.
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.	

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11. Lanthanum carbonate for adult chronic kidney disease (CKD) patients with hyperphosphataemia who are on dialysis and are not adequately controlled on calcium

Application

11.1. The Committee reviewed the application from Takeda New Zealand Limited for the treatment of adult chronic kidney disease (CKD) patients with hyperphosphataemia who are on dialysis and are not adequately controlled on calcium.

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 the funding application for lanthanum carbonate be **declined**. In making this recommendation, the Committee considered:

- the evidence that was consistent with only a modest clinically meaningful health benefit of lanthanum carbonate with some difficulty in translating into the New Zealand setting

- the high-quality evidence that shows no benefit of lanthanum carbonate over calcium carbonate

11.4. The Committee requested advice from the Nephrology Advisory Committee regarding interpretation of evidence, specifically regarding the health benefit of lanthanum carbonate versus sevelamer carbonate, and whether there is a subgroup of individuals who would benefit from lanthanum carbonate, such as those contraindicated to using, or refractory to, calcium carbonate, including patient number estimates for this population.

Discussion

Māori impact

11.5. The Committee considered that hyperphosphataemia in adult CKD patients who are on dialysis and are not adequately controlled on calcium disproportionally affect Māori.

Discussion

11.6. The Committee noted that Pharmac have received funding applications for sevelamer hydrochloride and sevelamer carbonate for the treatment of hyperphosphataemia in patients with CKD.

11.7. The Committee noted that PTAC and the Nephrology Advisory Committee reviewed an application and a number of resubmissions for sevelamer hydrochloride (submitted by Sanofi New Zealand) on several occasions (PTAC February 2013, PTAC November 2013, Nephrology Subcommittee December 2014). The Committee noted that PTAC and the Nephrology Advisory Committee both recommended the application be declined due to poor quality evidence and safety concerns. At that time, PTAC and the Nephrology Advisory Committee noted that the carbonate formulation of sevelamer could have a better safety profile than the hydrochloride formulation and suggested that a funding application for sevelamer carbonate be submitted.

11.8. The Committee noted that an application for sevelamer carbonate was received from Sanofi in August 2016. The Committee noted that sevelamer carbonate is currently under assessment, and that the Nephrology Advisory Committee recommended the application for medium priority, and PTAC recommended the application for low priority.

11.9. The Committee noted that hyperphosphataemia is defined as having serum phosphorous levels of greater than 1.46mmol/L (>4.5mg/dL), which may present as clinically asymptomatic or symptomatic. The Committee noted that the most common symptoms include bone pain, fractures, joint pain, pruritus, or rash, and that prolonged hyperphosphataemia in CKD patients can lead to cardiovascular calcification, metabolic bone disease, and the development of secondary hyperparathyroidism. The Committee noted that these symptoms contribute to a reduced quality of life, which worsens with increasing CKD severity grade, and is significantly influenced by age, gender, diabetes and history of cardiovascular co-morbidities (Mujais et al. Clin J Am Soc Nephrol. 2009;4:1293-301).

11.10. The Committee noted that there is a well-established association between hyperphosphataemia and increased morbidity and mortality in patients with CKD and undergoing dialysis (Askar et al. Saudi Med J. 2015;36:13-9; Cozzolino et al. Toxins (Basel). 2019;11:213; Haider et al. PLoS One. 2015;10; Palmer et al. JAMA 2011;305:1119-27). The Committee noted that hyperphosphataemia is considered inevitable among patients with end stage renal disease (ESRD) due to the extent of renal impairment associated with this condition and is present in the majority of dialysis patients (Hutchison. Kidney Int. 2009;75:906-14), therefore adjunct treatment with a phosphate-binding agent is generally required (Achinger et al. Kidney International. 2005;67:S28-S32). The Committee noted that dialysis patients in general are in extremely poor health, with significantly reduced survival relative to the general population. Overall, the Committee considered there is a high health need for this patient group.

11.11. The Committee noted that Data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) reported that there were 2,855 patients (2000 on haemodialysis, 855 on peritoneal dialysis) receiving dialysis in New Zealand in 2019 (ANZDATA 43rd Annual Report 2020). The Committee noted that ANZDATA survival data is not stratified by the presence of hyperphosphataemia, however, between 75% and 90% of patients on dialysis are treated with phosphate binders, suggesting that

approximately 2,500 individuals on dialysis will receive treatment for hyperphosphataemia each year in New Zealand (St Peter, et al. Am J Kidney Dis. 2018;71:246-53; Lopes et al. Am J Kidney Dis. 2012;60:90-101). The Committee considered this patient estimate to be appropriate. The Committee also noted that ANZDATA estimates a median survival of between 7.6 years (in patients aged 25 to 44) to 1.7 years (in patients aged 85 and above) among dialysis patients in New Zealand between 2010 to 2019 (ANZDATA 43rd Annual Report 2020).

11.12. The Committee noted that CKD disproportionally affects Māori (Walker 2019 et al. Semin Nephrol. 2019;39:297-299), which was previously acknowledged by PTAC in their evaluation of sevelamer carbonate (August 2019 PTAC minutes, paragraph 11.9). The Committee noted that Māori also experience a higher incidence of diabetic and hypertensive ESRD, which cannot be fully explained by the underlying CKD prevalence (Walker 2019 et al. Semin Nephrol. 2019;39:297-299). The Committee also noted that between 2015 and 2019 Māori people were three to four times more likely to be on dialysis than non-Māori, non-Pacific peoples (ANZDATA 43rd Annual Report 2020). The Committee noted that other factors that may contribute to this difference in incidence are socio-economic disadvantage, which is a known risk factor for ESRD, and underutilisation of medical services (Walker 2019 et al. Semin Nephrol. 2019;39:297-299). The Committee also noted that Pacific peoples, people living in rural and remote areas, as well as people with a low socioeconomic status are disproportionately affected by CKD and in turn hyperphosphataemia. Members considered that access to medication may also influence the outcomes in these patient populations.

11.13. The Committee noted that hyperphosphataemia in patients with CKD and on dialysis is currently treated with phosphate-binding agents in conjunction with dietary phosphate restriction or limiting dietary phosphate intake alone. The Committee noted that there are two phosphate binding products funded in New Zealand: aluminium hydroxide and calcium carbonate, however, aluminium hydroxide is not recommended as there are concerns regarding the toxicity of absorbed aluminium. The Committee noted that other treatments that are not currently funded in New Zealand include sevelamer (hydrochloride and carbonate), calcium acetate, lanthanum carbonate, and sucroferric oxyhydroxide (Chan et al. Aust Prescri. 2017;40:10-14). Given the currently funded treatment options, the Committee considered that there may be an unmet health need for those who are contraindicated to using or inadequately controlled on calcium carbonate, however, were unsure of the number of individuals this would apply to.

11.14. The Committee noted that lanthanum carbonate is a non-aluminium, non-calcium-based phosphate binder that forms insoluble lanthanum phosphate complexes that pass through the gastrointestinal (GI) tract unabsorbed, reducing phosphate absorption. The Committee noted that lanthanum carbonate is Medsafe approved for the treatment of CKD patients with hyperphosphataemia on dialysis. The Committee noted that dosing is individualised to achieve acceptable serum phosphate levels, with a recommended starting dose of 750mg daily, titrated every 2-3 weeks up to a maximum of 3750mg daily, and that most patients will require a dose of between 1500mg to 3000mg daily.

11.15. The Committee noted that the key evidence for lanthanum carbonate in the treatment of hyperphosphataemia in patients with CKD comes from four clinical trials:

11.15.1. The Committee noted that the NCT01578200 (Ogata 2021) trial was an open-label, randomized, parallel-group clinical trial which investigated lanthanum carbonate compared to calcium carbonate in 2309 patients with CKD, hyperphosphataemia, and one or more risk factors for vascular calcification. The Committee noted that after a median duration of follow up of 3.16 years, composite cardiovascular events occurred in 13.8% of those in the lanthanum carbonate group versus 12.5% of those in the calcium carbonate group, and overall there was no significant difference in all cause death (Ogata et al. JAMA. 2021;18:1946-1954.).

11.15.2. The Committee noted that the NCT00441545 (Sprague 2009) trial was a prospective, multicentre, open-label, randomised, cross-over study which investigated lanthanum carbonate compared to sevelamer hydrochloride in 182 patients with CKD undergoing stable haemodialysis 2-3 times weekly for at least two months. The Committee noted that after four weeks of randomised crossover treatment, serum phosphorus levels had decreased by 1.7 ± 0.1mg/dl in the lanthanum carbonate group versus a decrease of 1.4 ± 0.1mg/dl in the sevelamer hydrochloride group. The Committee noted that serum calcium had a mean increase of 0.1 ± 0.1mg/dl in the lanthanum carbonate group versus a mean decrease of 0.1 ± 0.1mg/dl in the sevelamer carbonate group (P=0.025), and that intact parathyroid hormone (iPTH) had a mean increase of 296.1 ± 16.4pg/mL in the lanthanum carbonate group versus a mean increase of 286.9 ± 16.4pg/mL in the sevelamer hydrochloride group (P=0.552) (Sprague et al. Clin Nephrol. 2009;72:252-258.).

11.15.3. The Committee noted that the Kasai 2012 trial is a prospective, randomised, open blinded, endpoint (PROBE), crossover study which investigated lanthanum carbonate compared to sevelamer hydrochloride in 41 patients undergoing haemodialysis for at least three months. The Committee noted that after 13 weeks of randomised crossover treatment, the mean difference in serum phosphate was −0.3mg/dL (95% CI not reached [NR]; P=0.09), the mean difference in serum calcium was 0.1mg/dL (95% CI NR; P=0.47), and the mean difference in iPTH was 14.3pg/mL (95% CI NR; P=0.48), where a mean difference of <0 favours lanthanum carbonate (Kasai et al. Ther Apher Dial. 2012; 16:341-349.).

11.15.4. The Committee noted that the EPISODE trial is a randomised, open label, multicentre, interventional trial which investigated lanthanum carbonate compared to sucroferric oxyhydroxide in 160 patients on dialysis. The Committee noted that after 12 months of treatment, 14.5% of the lanthanum carbonate group showed decreased coronary artery calcification (CAC) scores versus 28.3% in the sucroferric oxyhydroxide group, however that there was no significant difference in percentage change in CAC between the two groups. The Committee noted that serum phosphate levels had decreased by 0.57 ± 1.45mg/dL in the lanthanum carbonate group versus a decrease of 0.82 ± 1.33mg/dL in the sucroferric oxyhydroxide group (Isaka et al. J Am Soc Nephrol. 2021;32:723-735.).

11.15.5. The Committee noted that the adverse events reported across the various trials were predominantly GI-related. The Committee noted that in the Ogata 2021 trial, 25.7% of patients in the lanthanum carbonate group experienced GI-related side effects versus 23.4% in the calcium carbonate group. The Committee noted that other common adverse effects included infections and infestations (16.0% versus 13.9%), skin and subcutaneous tissue disorders (14.5% versus 17.0%), and metabolism and nutrition disorders (10.6% versus 18.5%) in the lanthanum carbonate and calcium carbonate groups respectively. The Committee also noted that the lanthanum carbonate group had a higher risk of cardiovascular death (HR 1.51) and a higher all-cause mortality (HR 1.10) than the calcium carbonate group. (Ogata et al. JAMA. 2021;18:1946-1954.).

11.16. The Committee considered that the evidence provided shows that lanthanum carbonate does not provide a strong additional health benefit over the comparators investigated. The Committee considered the following during their critical appraisal of the evidence:

11.16.1. The Committee considered that the Ogata 2021 trial provided strong quality of evidence, however that this evidence showed numerically worse outcomes in lanthanum carbonate compared to calcium carbonate.

11.16.2. The Committee considered that the results of the Sprague 2009 trial showed that both lanthanum carbonate and sevelamer hydrochloride reduce phosphate levels, but that neither treatment was superior.

11.16.3. The Committee considered that although the EPISODE and Kasai 2012 trials showed that lanthanum carbonate provided a moderate improvement versus comparators, they are of weak quality and have poor generalisation to the New Zealand population. The Committee considered that the results of these studies are difficult to translate to the New Zealand population as both trials were conducted in a Japanese population with low rates of diabetes, and the comparators (sucroferric oxyhydroxide and sevelamer hydrochloride) are not currently available treatments in New Zealand. Additionally, the Committee considered that the outcome measured in the EPISODE trial (percentage change in CAC score) is difficult to interpret in terms of clinically meaningful outcomes in the New Zealand setting in people with ESRD, and that the small population size in the Kasai 2012 trial (n=41) leads to low statistical power.

11.17. The Committee was made aware of the ongoing PHOSPHATE trial: A randomised, interventional trial investigating whether reduction of serum phosphate concentration toward the normal level with phosphate-lowering medications reduces the risk of cardiovascular death or non-fatal major cardiovascular events; improves physical health, fatigue, and patient satisfaction in kidney failure patients receiving dialysis; and is cost-effective. The Committee noted that the trial includes 3600 participants in Australia, New Zealand, Canada and UK (600 in Australia and New Zealand) with kidney failure and on dialysis aged over 45 years or over 18 years with diabetes (Australasia Kidney Trials Network). The Committee considered it would be appropriate to follow the results of this trial to help inform future funding decisions in this area.

11.18. The Committee noted that lanthanum carbonate is provided as a chewable tablet, and therefore provides a suitability benefit for patients with swallowing difficulties and those with restricted fluid intake. The Committee noted that there is currently no Medsafe-approved chewable tablet for sevelamer carbonate, therefore lanthanum carbonate also provides benefit over this product.

11.19. The Committee noted that lanthanum carbonate is more expensive than calcium carbonate, with no additional health benefit over this currently available treatment. The Committee considered that there may be changes in health sector expenditure, however that it was not possible to accurately define what these would be compared to currently funded treatments. The Committee also considered that the uptake of lanthanum carbonate would be the patient group who are uncontrolled on calcium carbonate.

11.20. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for lanthanum carbonate if it were to be funded in New Zealand for CKD patients with hyperphosphataemia. 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	Adult chronic kidney disease (CKD) patients with hyperphosphataemia who are on dialysis and are not adequately controlled on a calcium binder and expected to be on dialysis for greater than 12 months.
Intervention	Lanthanum carbonate. Initially 750mg once daily, increasing as necessary every 2 to 3 weeks until acceptable serum phosphate levels are achieved and maintained (usually between 1500mg to 3000mg once daily).
Comparator(s) (NZ context)	Calcium carbonate (currently available)
Outcome(s)	Reduction in phosphate levels. Based on reduction in phosphate, could extrapolate to assume: • Reduction in risk of premature mortality • Reduction in fractures • Reduction in cardiovascular events • Improvement in quality of life

Table definitions:

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

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

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

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

I certify that this is a true and correct record of the minutes of the meeting held on held 18 & 19 November 2021

Signed: _____ Date: 6/02/2022

Doctor Jane Thomas, Chair