PTAC Pharmacology and Therapeutics Advisory Committee

Objective advice to PHARMAC

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

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

Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 20 and 21 May 2021

The records of PTAC and Subcommittees of PTAC are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016. Note that this document is not necessarily a complete record of the meeting; only the relevant portions of the record relating to discussions about an Application or Pharmac staff proposal that contain a recommendation are generally published.

PTAC and Subcommittees of PTAC may:

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

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

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

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

Chair

Present:

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

Apologies
None noted

_____
Chair

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

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

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

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

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

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

2. Previous Meeting Record

2.1. The meeting record of the February 18 & 19 2021 meeting were accepted as read.

3. Subcommittee Records

Combined Neurological and Rare Disorders Subcommittee Record

3.1. The Committee noted the record of the Rare Disorders and Neurological Subcommittees' combined meeting held on 5 March 2021.

3.2. The Committee acknowledged the discussion of the Subcommittees and their recommendation for funding of risdiplam for spinal muscular atrophy (SMA) Type 1 with a high priority.

3.3. The Committee noted that data with longer follow up data for risdiplam in SMA Type 2 and 3 has recently become available, subsequent to the combined Subcommittees' meeting.

3.4. The Committee stated it would like to review the updated evidence for risdiplam, as well as relevant information for nusinersen and onasemnogene abeparvovec-xioi (a gene therapy for SMA, marketed as Zolgensma).

3.5. The Committee considered it would also like to review the Special Authority criteria recommended by the Subcommittees, noting that the Subcommittees' recommended criteria were provisional.

Cancer Treatment Subcommittee (February 2021)

3.6. The Committee noted the record of the Cancer Treatments Subcommittee of PTAC (CaTSoP) meeting held on 15 February, which included recommendations regarding the following funding applications:

- rituximab for precursor B-call acute lymphoblastic leukaemia
- olaparib for ovarian, fallopian or primary peritoneal cancer, newly diagnosed, BRCA-mutated, platinum sensitive – maintenance.

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

3.8. In regards to item 4 and CaTSoP's consideration of rituximab for precursor B-Cell acute lymphoblastic leukaemia:

3.8.1. The Committee noted the Subcommittee's low priority recommendation for people with precursor B-Cell acute lymphoblastic leukaemia and its medium priority recommendation for people with precursor B-Cell acute lymphoblastic leukaemia and CD20 expression.

3.8.2. The Committee considered that prevention of relapse was important for this patient group and that there was evidence supporting a reduction in the relapse rate with the addition of rituximab to chemotherapy for this patient group. The Committee considered that while the evidence was of weak strength, the health need of this patient group was high and the cost of rituximab was low compared with other novel agents.

3.9. In regards to item 5 and CaTSoP's consideration of olaparib for ovarian, fallopian or primary peritoneal cancer, newly diagnosed, BRCA-mutated, platinum sensitive – maintenance:

3.9.1. The Committee noted the Subcommittee's high priority recommendation for this application. The Committee acknowledged that in doing so CaTSoP had addressed the questions that remained from PTAC's prior review of olaparib.

3.9.2. The Committee noted that it had considered olaparib for ovarian, fallopian or primary peritoneal cancer, newly diagnosed, BRCA-mutated, platinum sensitive – maintenance in August 2020 and recommended funding with a medium priority.

3.9.3. The Committee noted that there was evidence of treatment benefit for people with somatic BRCAm and HRD-positive ovarian cancers; however these subgroups were not included in the proposed access criteria due to possible equity concerns regarding access to diagnostic testing and consistency in phenotypic definitions. The Committee considered that should treatment be funded for these subgroups, early engagement with pathology services would be beneficial, in particular to understand the potential impact funding could have on health services due to diagnostic testing requirements.

3.9.4. The Committee considered the available evidence indicated greatest progression free survival benefit for patients with BRCAm ovarian cancers.

3.9.5. The Committee considered that uncertainty remained regarding the appropriate duration of maintenance treatment for patients who have a partial response to olaparib after two years, and considered further review of this may be appropriate in the event that further evidence is published that guides optimal duration of treatment.

4. Matters Arising - Quinacrine for SLE

Discussion

4.1. The Committee considered correspondence from the applicant of a funding application for quinacrine for systemic lupus erythematosus (SLE). The Committee noted it had considered quinacrine for SLE at its November 2020 meeting and had recommended it be declined. The Committee noted the applicant's response regarding the review of quinacrine for SLE.

4.2. The Committee agreed with the applicant's comments regarding an unmet health need in people with SLE and considered there is an unmet health need in people with SLE. However, the Committee considered it was unlikely this unmet health need would be addressed by quinacrine, as there was little identifiable high quality evidence to support its efficacy and the Committee considered there was still a lack of quinacrine-specific evidence able to be presented in the applicant's response.

4.3. The Committee noted the clinical risks of quinacrine in this setting, and that this agent is not Medsafe-approved for any use in New Zealand, and its adverse event profile differences compared with the currently funded options, primarily the risk of aplastic anaemia.

4.4. The Committee noted the evidence regarding methotrexate provided by the applicant and that the use of quinacrine in SLE is commented on in the 2019 updated EULAR guidelines. However, the Committee considered the evidence for the use of quinacrine was limited quality, with most of the evidence consisting of case reports or case series with a high risk of bias with respect to the clinical effect.

4.5. The Committee considered the group of people with hydroxychloroquine intolerance would likely be a relatively large group. The Committee considered the side effect profile for individuals with an allergy to hydroxychloroquine may experience similar adverse effects skin changes and anaphylaxis, with quinacrine.

4.6. The Committee did not consider it necessary to re-review the application. The Committee based this on the limited evidence available, the potential adverse effect profile, and lack of a Medsafe-approved product.

5. Correspondence

5.1. The Committee reviewed correspondence from Canterbury District Health Board and the Urological Society of Australia and New Zealand in regard to mirabegron for the treatment of overactive bladder.

5.2. The Committee noted that in August 2019, PTAC had reviewed a funding application for mirabegron for the treatment of overactive bladder. The Committee noted that, in August 2019, PTAC had recommend that mirabegron be funded only if cost-neutral to oxybutynin due to a similar health benefit compared to currently funded agents.

5.3. The Committee noted that the supplier discontinuation of oxybutynin results in a reduction in appropriate first-line treatment options.

5.4. The Committee noted that the correspondence received outlined opinion that intravesical clostridium botulinum type A toxin (botulinum toxin) is the current second line treatment for overactive bladder, rather than oral anti-muscarinic anti-cholinergic agents, and that as such, it should be considered the relevant comparator for the mirabegron application. The Committee noted the request that the health sector cost and burden of botulinum toxin injection should also be considered in the cost-neutrality analysis.

5.5. The Committee did not consider the information provided in the correspondence would influence an updated recommendation for the mirabegron funding application. However, the Committee considered that additional evidence regarding the place of botulinum toxin, other treatment alternatives and treatment sequencing would be useful in any further assessment of this application and consideration of the appropriate cost-neutral comparator.

6. Rituximab for IgG4 disease

Application

6.1. The Committee reviewed the clinician application for rituximab for the treatment of IgG4 related disease.

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

Recommendation

6.3. The Committee recommended that rituximab for the treatment of IgG4 related disease be listed with a high priority, subject to the following Special Authority criteria:

Initial application – Immunoglobulin G4-related disease (IgG4-RD)
Application from any relevant practitioner. Approvals valid for 6 weeks for applications meeting the following criteria:
All of the following:

1. Patient has confirmed diagnosis of IgG4-RD; and
2. Either:
    2.1. Treatment with corticosteroids and/or disease modifying anti-rheumatic drugs for at least a period of 3 months has been ineffective in lowering corticosteroid dose below 5 mg per day (prednisone equivalent) without relapse; or
    2.2. Treatment with corticosteroids and/or disease modifying anti-rheumatic drugs is contraindicated or associated with evidence of toxicity or intolerance; and
3. Total rituximab dose used should not exceed a maximum of two 1000 mg infusions of rituximab given two weeks apart.

Renewal – Immunoglobulin G4-related disease (IgG4-RD)
Application from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:

1. Either:
    1.1. Treatment with rituximab was previously successful and patient has demonstrated sustained response, but the condition has relapsed; or
    1.2. Patient is receiving maintenance treatment; and
2. Rituximab re-treatment not to be given within 6 months of previous course of treatment; and
3. Maximum of two 1000 mg infusions of rituximab given two weeks apart

6.4. In making the above recommendation, the Committee considered the high health need for this patient group, the toxicity of currently available alternative treatments for IgG4 related disease, the strong evidence of biological plausibility of benefit with rituximab despite moderate quality evidence based on cohort studies, and the potential to slow progression of disease when treated early.

Discussion

6.5. The Committee noted that immunoglobulin G4 (IgG4) related disease is a recently-recognised immune-mediated fibroinflammatory condition of unknown aetiology with a diverse phenotype that can affect multiple organs and body systems, most commonly manifesting as type 1 (IgG4-related) autoimmune pancreatitis; sclerosing cholangitis, typically occurring together with type 1 autoimmune pancreatitis; salivary gland enlargement or sclerosing sialadenitis similar to Mikulicz disease; orbital disease, often with proptosis; retroperitoneal fibrosis, frequently with chronic periaortitis and often affecting the ureters, leading to hydronephrosis and renal injury. The Committee considered that diagnosis of IgG4 related disease was difficult however there was an increasing awareness and the American College of Rheumatology/European League Against Rheumatism have developed a complex classification process which includes a complete list of exclusions and inclusions.

6.6. The Committee noted that IgG4-affected organs share several core pathologic features and clinical and serologic similarities, including tumour-like swelling, presence of a lymphoplasmacytic infiltrate enriched in IgG4-positive plasma cells, and a variable degree of fibrosis that has a characteristic "storiform" pattern. The Committee noted that serum IgG4 concentrations can be elevated (defined as >135 mg/dL, >121 mg/dL, or >86 mg/dL depending upon the laboratory) in approximately two-thirds of patients. The Committee considered that the diagnosis usually depends on radiological features noting that serum IgG4 levels cannot be relied on for diagnosis.

6.7. The Committee noted that IgG4-related disease has historically had low reported incidence, likely related to difficulty in making this diagnosis, however, patient numbers have increased over time with increasing awareness of IgG4-disease, including incorporating reclassification

of other diseases. The Committee considered that most epidemiological information regarding IgG4-related disease comes from studies conducted in Japan and China, where incidence is reported to be between 0.3 and 1.0 per 100,000 per year. The Committee considered that, based on this incidence, it is likely that there would be between 15 and 50 new cases per year in New Zealand. The Committee considered that the incidence is likely to be at the lower end of this range but may rise over time as IgG4-related disease becomes more commonly recognized.

6.8. The Committee noted that current treatment for IgG4-related disease typically starts with corticosteroids as first-line treatment with disease usually responding rapidly to treatment unless there is significant fibrosis, noting that fibrosis increases in severity if the diagnosis is delayed. The Committee noted loss of disease response is common once corticosteroids are tapered to low doses, and long-term corticosteroid treatment can lead to substantial toxicity, in particular in patients presenting with autoimmune pancreatitis who are at high risk of diabetes. The Committee noted severe disease may require urgent, high dose corticosteroids.

6.9. The Committee noted that treatment with conventional immunomodulators (cyclophosphamide or mycophenolate) is considered for patients who cannot tolerate or have not responded to high dose corticosteroids however these have only a modest effect and are associated with significant adverse effects. Committee considered that the health need for patients with IgG4-related disease is high for those with severe illness experiencing frequent relapse.

6.10. The Committee noted a non-randomised trial of low-dose (50 to 100 mg per day) cyclophosphamide in combination with corticosteroid in 102 patients with IgG4-related disease, compared with corticosteroid monotherapy (Yunyun et al. Sci Rep. 2017;7:6195). The Committee noted that at one-year follow-up 38.5% of patients receiving corticosteroid monotherapy had relapsed, compared to a 12% in those who also received combination cyclophosphamide. The Committee noted that the corticosteroid regimen resulted in a new diagnosis of type II diabetes mellitus in approximately 10% of participants, however low-dose cyclophosphamide was reported to be relatively well tolerated without any events of bone marrow suppression. The Committee noted that there was no attempt to lower corticosteroid doses below 10 mg/day over the course of the trial.

6.11. The Committee noted a randomised non-blinded trial investigating the use of corticosteroid monotherapy compared with combination therapy of corticosteroid with mycophenolate (1000 to 1500 mg/day) in 69 patients with IgG4-related disease (Yunyun et al. Rheumatology (Oxford). 2019;58:52-60). The Committee noted that patients were more likely to experience remission on combination therapy (76% on combination therapy vs 40% on corticosteroids alone). The Committee noted that this study also made no attempt to lower corticosteroid doses.

6.12. The Committee noted a retrospective multicentre study investigating the long-term efficacy and safety of rituximab in IgG4-related disease using data from a French nationwide study of 33 patients treated either with 2 doses of 1000 mg rituximab separated by 15 days (25 patients), 4 weekly doses of 375 mg/m2 (six patients), and other regimens in 2 patients (4 weekly doses of 150 mg/m2 or 2 doses of 375 mg/m2 separated by 15 days) (Ebbo et al. PLoS One. 2017;12:e0183844). The Committee noted that despite variability in treatment regimen, the durability of clinical remission persisted for at least six months for most patients, and in some cases extended beyond 18 months. The Committee noted that a clinical response was observed in 29 of the 31 patients in the study, and that patients received maintenance treatment, at treating clinician's discretion, between one to 17 months after initial treatment with rituximab. The Committee noted that the probability of relapse-free survival was higher with rituximab maintenance than without (p=0.016). The Committee noted that there were nine severe infections during the course of the study and no deaths.

6.13. The Committee noted a prospective, open-label trial of patients with active disease defined by the IgG4-RD Responder Index treated with two doses of rituximab (1000 mg each

dose) (Carruthers et al. Ann Rheum Dis. 2015;74:1171-7). The Committee noted that of the 30 patients included in the study, 27 patients had discontinued corticosteroid use at 12 months, and 60% of patients achieved complete remission. The Committee noted that 19 patients had elevated baseline serum IgG4 concentrations with a mean concentration of 911 mg/dL (range 138–4780 mg/dL), which declined to 422 mg/dL (range 56–2410 mg/dL) at month 6 following rituximab treatment ($p<0.05$). The Committee noted that 42% of patients in the study achieved normal IgG4 serum levels and considered that these results were unlikely to be achievable with immunomodulator treatment.

6.14. The Committee noted a study on the long-term efficacy of maintenance therapy with rituximab for IgG4-related disease in 14 patients either treated on relapse or every 6 months as maintenance (either 1000 or 2000 mg) (Campochiaro et al. Eur J Intern Med. 2020;74:92-8). The Committee noted that 100% of patients undergoing maintenance treatment were relapse-free at 18 months, compared with 29% in the group only treated at relapse ($p=0.006$).

6.15. The Committee noted that one of the most common presentations of IgG4-related disease is autoimmune pancreatitis and noted a Mayo clinic study describing the experience of treating relapsing autoimmune pancreatitis with immunomodulators and rituximab (Hart et al. Gut. 2013;62:1607-15). The Committee noted that during a median follow-up of 47 months, 52 of 116 autoimmune pancreatitis patients, who were all treated with corticosteroids and immunomodulators, experienced 76 relapse episodes. The Committee noted that first relapses were treated with a course of corticosteroids in 24 patients, and with corticosteroids plus immunomodulators in another 27 patients and noted that the subsequent relapse-free survival was similar between the two groups ($p=0.23$). The Committee noted that 38 patients received an immunomodulator for more than 2 months, and that failure or intolerance of immunomodulator therapy occurred in 45% of patients. The Committee noted that 12 patients with corticosteroid or immunomodulator intolerance/resistance were subsequently treated with rituximab, with 83% of those patients experiencing complete remission without relapse while on maintenance therapy.

6.16. The Committee noted a study investigating the clinical phenotypes of IgG4-related disease and how these affect different prognostic outcomes (Lanzillotta et al. Rheumatology (Oxford). 2020;59:2435-42). The Committee noted that patients with biliary involvement had higher relapse rates than other groups and were more likely to develop diabetes mellitus (in 62%, compared with 7% of patients with retroperitoneum/aortitis disease, 21% of patients with head and neck limited IgG4-related disease, and 31% with Mikulicz/systemic disease).

6.17. The Committee noted another Mayo clinic study investigating the effects of rituximab with or without maintenance on rate of relapse of pancreaticobiliary IgG4-related disease (Majumder et al. Clin Gastroenterol Hepatol. 2018;16:1947-53). The Committee noted that a higher proportion of patients experience relapse in the group without maintenance therapy (3-year event rate 45% vs 11% with rituximab maintenance therapy; P=0.034). The Committee noted that dosing for the maintenance group was variable, with patients receiving 2 g of rituximab every 2-6 months. The Committee noted that patients in this study who did not experience an adequate therapeutic effect were more likely to have biliary involvement, while patients with classic autoimmune pancreatitis were more likely to experience good effect. The Committee considered that delaying treatment appears to reduce the success of rituximab treatment, with the most benefit seen in patients who have not developed significant fibrosis at the time of rituximab treatment.

6.18. The Committee also noted the following evidence for rituximab for the treatment of IgG4-related disease:

- Maritati et al. Rheumatology (Oxford). 2020;59(Suppl 3):iii123-iii131
- Detiger et al. Acta Ophthalmol. 2019;97:451-59
- Betancur-Vásquez et al. Reumatol Clin. 2020;16:195-202
- Khosroshahi et al. Medicine (Baltimore). 2012;91:57-66
- Khosroshahi et al. Arthritis Rheum. 2010;62:1755-62

- Omar et al. Rheumatology (Oxford). 2020;59:718-26
- Quattrocchio et al. Oncotarget. 2018;9:21337-47

6.19. The Committee considered that the evidence of effectiveness for rituximab in IgG4-related disease was of weak to moderate quality, noting rituximab is often trialled in patients with a wide range of uncommon autoimmune conditions in small cohort and case studies, and considered that it is unlikely that any large-scale clinical trials will be published in these populations due to low patient numbers. However, the Committee considered there was strong biological plausibility of effect and likelihood for response of rituximab in the treatment of IgG4-related disease, particularly compared with currently available treatments.

6.20. The Committee noted that the dosing of rituximab for IgG4-related disease should not exceed 2000 mg every six months and considered that 1000 mg every six months is likely to be sufficient for most patients, noting that the evidence suggests that there may be a clinically significant benefit for maintenance treatment in preventing relapse. The Committee considered that if rituximab were to be funded for IgG4-related disease, there may be a reduction in long term disease progression for some patients including organ damage in pancreatic, renal, aortic, and liver disease, as well as the possibility of reduction in incidence of diabetes associated with systemic corticosteroid treatment, and that this would be of benefit to the health system. Members acknowledged there is a lack of evidence to confirm reduction in long term organ damage.

6.21. The Committee considered that it would be beneficial for patients to be treated with rituximab as soon as possible if relapse occurs following initial corticosteroid treatment, due to the toxicity associated with long-term use of the alternative agents (corticosteroids and immunomodulators). The Committee noted that rituximab is associated with some adverse events but considered that these are well known and manageable.

6.22. The Committee considered that the optimal number of courses and dose of rituximab for the treatment of IgG4-related disease is unknown, due to the variable dosing schedules in rituximab trials for various indications; noted that in some settings that patients receive rituximab re-treatment only at relapse; and considered that rituximab may be used similarly in the setting of IgG4-related disease. The Committee considered that as the evidence for the benefit associated with maintenance rituximab continues to develop, more patients may seek maintenance treatment 6 monthly, for a durable response. The Committee noted that patients who relapse early in the treatment cycle would typically be re-treated initially, however if relapse continues to occur shortly after treatment with rituximab this would indicate poor response to treatment prompting cessation.

6.23. The Committee considered that the information included in the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information table is realistic for rituximab if it were to be funded in New Zealand for IgG4-related disease. 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 IgG4-related disease who have relapsed after one course of glucocorticoids and/or immunomodulators.
Intervention	Rituximab administered intravenously as a loading a dose of 2x 1doses 15 days apart (2 doses total) initially, then 1-2 g six-monthly for as maintenance if necessary.
Comparator(s) (NZ context)	Prednisone (40mg/day for 28 days, per Carruthers et al. 2015) or IV methylprednisone, for 93.9% of patients (the proportion who received glucocorticoids), or DMARD treatment for 39.4% of patients (composed of: azathioprine 2mg/kg/day (27.3%) or methotrexate 20mg/week (12.1%), mycophenolate mofetil 1-1.5g/day (3%) or cyclophosphamide 50-100mg/day (3%) [proportions sourced from Ebbo et al. 2017])
Outcome(s)	• Relapse-free survival (Ebbo et al. 2017) • Disease remission (Carruthers et al. 2015) • Improved IgG4-RD ≥2 points (Ebbo et al. 2017) • Reduced corticosteroid use (Carruthers et al. 2015) • Frequency of adverse events, which include: serious infections, hypogammaglobulinemia, glucose intolerance, newly diagnosed or aggravation of diabetes mellites, infection, and liver or kidney damage (Omar et al. 2020) • Possible delayed progression to end-stage organ damage
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.	

7. Zoledronic acid - Treatment of moderate to severe hypercalcaemia

Application

7.1. The Committee reviewed the clinician application for zoledronic acid in the treatment of moderate to severe hypercalcaemia.

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

Recommendation

7.3. The Committee **recommended** that zoledronic acid for moderate to severe hypercalcaemia of any cause be listed with a **high priority.** The Committee recommended the following addition to the Special Authority for zoledronic acid (new criteria only shown):

> **Zoledronic acid**
> **Initial application** — (hypercalcaemia) from any relevant practitioner. Approvals valid without further renewal unless notified for applications meeting the following criteria:
> 1 Patient has symptomatic hypercalcaemia.

7.4. In making this recommendation, the Committee considered: the unmet health need of patients with hypercalcaemia, the greater suitability of zoledronic acid compared with to currently funded alternatives, and the potential savings to the healthcare sector and reduction of infusion service use from zoledronic acid. The Committee also considered the inconsistent access to infusion services for patients in New Zealand requiring treatment infusions, the adverse renal events associated with zoledronic acid, and that zoledronic acid is not Medsafe-approved for this indication.

Discussion

7.5. The Committee considered that the application for moderate to severe hypercalcaemia sought funding for zoledronic acid for a very broad population that was challenging to define. The Committee noted that the application requested the funded access to zoledronic acid be widened to include patients with moderate to severe hypercalcaemia where no reversible cause is found.

7.6. The Committee considered severe hypercalcaemia is generally defined as a serum calcium concentration of > 3 mmol/L (Minisola et al., BMJ 2015;350:h2723).

7.7. The Committee considered the overall prevalence of hypercalcaemia is unclear. The Committee considered prevalence is best described for sub-populations prevalence of hypercalcaemia in people with primary hyperparathyroidism or malignancy. The Committee noted the estimated prevalence in the general population is 1:1,000 and that hypercalcaemia accounts for approximately 0.6% of all acute medical admissions (Turner. Clin Med (Lond). 2017;17:270-3).

7.8. The Committee noted approximately 90% of hypercalcaemia is due to primary hyperparathyroidism or malignancy (Minisola et al. BMJ 2015;350:h2723). The other 10% is due to other causes such as serum vitamin D related changes, endocrine disorders, spinal cord compression, other pharmaceutical treatments, immobilisation, and acute renal failure.

7.9. The Committee considered that the proportion of patients with hypercalcemia who present with overt hypercalcaemia symptoms was reducing because mild hypercalcaemia is commonly detected through routine laboratory testing.

7.10. The Committee considered there was an unmet health need for people with symptomatic hypercalcaemia, where the hypercalcaemia is not immediately remediable. The Committee considered the overall health need of patients with moderate to severe hypercalcaemia would depend more on the underlying condition rather than the hypercalcaemia itself. The Committee noted that hypercalcaemia caused by some conditions would resolve on treatment of the underlying disease but considered that treatment for hypercalcaemia may be needed in the interim (which can be lengthy depending on variable access and wait times for surgery).

7.11. The Committee considered that people with a range of underlying causes would benefit from zoledronic acid to treat symptomatic hypercalcaemia. This included patients where no reversible cause of hypercalcaemia could be found, and also as a ‘bridge’ to manage hypercalcaemia while patients await treatment of the underlying cause e.g. surgery.

7.12. The Committee were not aware of any evidence to inform the incidence and/or prevalence of hypercalcaemia in Māori or Pacific peoples. The Committee considered that, if Māori or Pacific people were disproportionately affected by hypercalcaemia, this would be as a result of the underlying condition. The Committee considered they were unable to identify any populations experiencing health disparities who would be affected disproportionately, based on the general epidemiology of the underlying diseases identified by the Committee.

7.13. The Committee noted that zoledronic acid is currently funded for several indications in the Pharmaceutical Schedule with two available formulations: Aclasta is funded with Special Authority restrictions for the treatment of patients with Paget’s disease, osteoporosis, and patients at risk of fracture as a result of receiving glucocorticoid therapy; and Zoledronic acid Mylan is funded with Special Authority restrictions for patients with bone metastases and early breast cancer.

7.14. The Committee noted that the applicant considered that currently, the patients being considered with moderate to severe hypercalcaemia would currently receive intravenous treatment with pamidronate; a bisphosphonate that is funded without restriction.

7.15. The Committee noted the following evidence for zoledronic acid:

- Safety of Intravenous Bisphosphonates for the Treatment of Hypercalcemia in Patients With Pre-existing Renal Dysfunction (Palmer et al. Ann Pharmacother. 2021;55:303-10). This retrospective analysis was conducted of IV pamidronate disodium and zoledronic acid in 113 adult patients with hypercalcaemia and creatinine clearance (CrCl) <60 mL/min. The primary endpoint of all-grade serum creatinine elevations occurred in 28 (24.8%) patients, with grade 3 or 4 serum creatinine elevations in 10.9% of patients treated with pamidronate disodium and 1.7% of patients receiving zoledronic acid. There

were no cases of osteonecrosis of the jaw and incidence of grade 1 or 2 hypocalcaemia was similar between treatment groups. Overall, 64.6% of patients achieved normalisation of corrected serum calcium by day 10, and there were no statistical differences between bisphosphonate type and renal function.

- Glucocorticoid sparing effect of zoledronic acid in sarcoid hypercalcemia (Kuchay et al. Arch Osteoporos. 2017;12:68). The authors report three cases of sarcoid hypercalcemia who were successfully managed with oral glucocorticoids for many months before developing adverse effects of glucocorticoids. When tapering of glucocorticoids was attempted, hypercalcemia recurred, so zoledronic acid was administered in order to control hypercalcemia and to allow tapering of glucocorticoids. Following zoledronic acid administration, serum calcium level normalised and glucocorticoids could be discontinued in all the three patients. Normocalcemia was maintained for an average of 18 months after a single infusion and sarcoidosis remained in remission in all the three patients.
- Short-Term Safety of Zoledronic Acid in Young Patients With Bone Disorders: An Extensive Institutional Experience (George et al. J Clin Endocrinol Metab. 2015;100:4163-71). This was a retrospective chart review of 81 inpatients and outpatients less than 21 years old who received at least one zoledronic acid infusion between 2010 and 2014 at a single hospital site. A total of 204 infusions were received. The most common indications were osteoporosis (33% of cohort), osteogenesis imperfecta (27.2%), chronic recurrent multifocal osteomyelitis (14.8%) and avascular necrosis (7.4%). Less than 5% of participants were diagnosed with each of the following: low bone mineral density, bone metastases, osteolytic lesions, fibrous dysplasia, vitamin D toxicity, cutis laxa, and fragility fracture not otherwise specified. Adverse events were mild and more common after the first infusion in patients with no previous bisphosphonate exposure. Adverse events included hypophosphatemia (25.2% of infusions), acute phase reactions (19.1%), and hypocalcaemia (16.4%). Symptomatic hypocalcaemia requiring intravenous calcium occurred after two infusions.
- Zoledronic acid in paediatric metabolic bone disorders (Bowden et al. Transl Pediatr. 2017;6:256-68). This review discusses the safety and use of zoledronic acid in childhood osteoporosis, chemotherapy-related osteonecrosis, hypercalcaemic disorders and malignant bone tumours.
- Acute unilateral anterior uveitis following zoledronic acid infusion: A case report (Anandasayanan et al. SAGE Open Med Case Rep. 2020;8:2050313X20944305). The authors describe the rare case of a 75-year-old female who presented with features of acute unilateral non-granulomatous anterior uveitis, which developed within 24 hours following the first dose of intravenous infusion of zoledronic acid administered to treat post-menopausal osteoporosis. She was treated with topical steroids and made an uneventful recovery in 2 weeks.
- Löfgren Syndrome with Hypercalcemia and Neuroendocrinological Involvement: A Case Report (Almaguer-Morales et al. Curr Rheumatol Rev. 2020;16:337-42). This case report discusses a 42-year-old woman with an atypical case of Löfgren Syndrome, a subtype of sarcoidosis occurring in 20-30% of cases. The patient was successfully treated in hospital with zoledronic acid and as an outpatient with immunosuppressive therapy.
- Intractable hypercalcaemia during pregnancy and the postpartum secondary to pathogenic variants in CYP24A1 (Arnold et al. Endocrinol Diabetes Metab Case Rep. 2019:19-0114). The authors report two cases of parathyroid-independent hypercalcaemia of pregnancy, due to biallelic loss of function of the P450 enzyme CYP24A1, the principal inactivator of 1,25(OH)2D results in hypervitaminosis D, hypercalcaemia and hypercalciuria. The second case was hypercalcaemic post-partum with a suppressed parathyroid hormone, normal 25(OH)D, and elevated 1,25(OH)2D levels. Her symptoms partially responded to intravenous saline and corticosteroids but bisphosphonates such as pamidronate disodium and zoledronic acid did not result in sustained improvement. Denosumab 120 mg subcutaneous injection successfully treated the hypercalcaemia, resolving completely 2 months post-partum.

- Use of Zoledronic Acid in a Neonate with Subcutaneous Fat Necrosis Complicated with Severe, Refractory Hypercalcemia (Militello et al. Am J Perinatol. 2019;36(S 02):S134-S138). Subcutaneous fat necrosis is a rare inflammatory disorder of the adipose tissue that may occur in the neonatal period. It is usually a self-limited condition; however, in complicated cases it can lead to severe and potentially life-threatening hypercalcemia. In this case, the serum calcium level reached 16.6 mg/dL. Standard treatment with intravenous fluids, furosemide and then methylprednisolone was not effective. Subsequently a single low dose of zoledronic acid was administered and ultimately managed the hypercalcemia.
- Zoledronic acid for neonatal subcutaneous fat necrosis (Di Bari et al. Clin Case Rep. 2017;5:567-9). An infant with subcutaneous fat necrosis and serum calcium of 15 mg/dL was treated with prednisolone and low-dose zoledronic acid. Serum calcium promptly normalised without rebound hypocalcaemia and redosing of zoledronic acid was not necessary.
- Life-Threatening Hypercalcemia During Prodrome of Pneumocystis jiroveci Pneumonia in an Immunocompetent Infant (VanSickle et al. Glob Pediatr Health. 2017;4:2333794X17705955). An 8-week-old girl with *Pneumocystis jiroveci* infection and life-threatening hypercalcemia (23.5 mg/dL) received Treatment with intravenous hydration, loop diuretic, and calcitonin which failed to correct the hypercalcemia. She was subsequently treated with zoledronic acid on 3 successive days (cumulative dose 0.375 mg) and serum calcium normalised on day 15.
- Life-Threatening Hypercalcemia due to Graves' Disease and Concomitant Adrenal Failure: A Case Report and Review of the Literature (Ozkaya et al. Case Rep Endocrinol. 2015;2015:684648).
- Systemic lupus erythematosus and hypercalcaemia: case report and brief review of the literature (Karageorgas et al. Scand J Rheumatol. 2011;40:408-9).
- The effect of intravenous zoledronic acid on glucocorticoid-induced multiple vertebral fractures in juvenile systemic lupus erythematosus (Souza et al. Rev Hosp Clin Fac Med Sao Paulo. 2004;59:302-5).

7.16. The Committee considered there to be no high-quality, clinical trial evidence for zoledronic acid in the treatment of non-malignant hypercalcaemia. However, the Committee considered it reasonable to extrapolate the evidence from zoledronic acid in hypercalcaemia of malignancy and its efficacy in reducing serum calcium, to hypercalcaemia of a non-malignant cause. Members noted a meta-analysis (Major et al. J Clin Oncol. 2001;19:558-67) of two RCTs, that reported zoledronic acid as superior to pamidronate in the treatment of hypercalcaemia of malignancy.

7.17. The Committee considered there is a level of class effect in the likely side effects among bisphosphonates, and noted the bulk of the evidence is for zoledronic acid due to its market share. The Committee noted the potential risk of osteonecrosis of the jaw (0.88-3.1% incidence) and anterior uveitis (Hoff et al., J Clin Oncol. 2006;24:18_suppl, 8528-8528) with intravenous pamidronate and/or zoledronic acid, but considered the risks associated with zoledronic acid would likely be the same or similar to the risks associated with pamidronate. The Committee considered the clinical risk of funding zoledronic acid for the treatment of moderate to severe hypercalcaemia was not greater than the current risk associated with pamidronate, noting pamidronate is listed with no restrictions.

7.18. The Committee considered that either the 4 or 5 mg presentation of zoledronic acid would be suitable for use in the treatment of moderate to severe hypercalcaemia. The Committee noted that neither presentation of zoledronic acid is Medsafe-approved for the considered indication. The Committee noted pamidronate was also not Medsafe-approved for this indication, and reiterated that clinicians need to exercise their clinical judgement when prescribing within their scope of practice for any medicine.

7.19. The Committee considered that approximately 1,000 patients per year would likely access zoledronic acid if it were funded for moderate to severe hypercalcaemia. The Committee considered patients currently receiving pamidronate infusions would all likely switch to zoledronic acid infusions, noting it is a faster infusion (fifteen minutes versus two hours) and is administered less frequently. The Committee considered the reduction in infusion time would provide significant benefit to the healthcare sector.

7.20. The Committee considered zoledronic acid would be used alongside a range of other pharmaceuticals; including glucocorticoids, intravenous fluids, and that cinacalcet or denosumab, which are not currently funded for hypercalcaemia, might also be considered, depending on the underlying condition, and considered it would replace pamidronate disodium.

7.21. The Committee considered some patients may remain on treatment for life if no underlying cause of hypercalcaemia is found. However, the Committee also considered some patients may use zoledronic acid as a short-term treatment, as a 'bridge' to more definitive treatment parathyroid surgery.

7.22. The Committee considered it likely zoledronic acid infusions would be repeated approximately every 4-6 weeks, based on the data on the use of zoledronic acid in the treatment of hypercalcaemia of malignancy. However, the Committee noted this would vary considerably, depending on the underlying disease and patient response. The Committee considered the broader population using zoledronic acid as a 'bridge' would likely receive 1 or 2 doses, while the lifelong patients would likely receive infusions every 4-6 weeks. The Committee considered that pamidronate can be dose titrated as it is available in three strengths, however the Committee considered it unlikely zoledronic acid would be dose titrated.

7.23. The Committee noted the data for pamidronate indicates the large majority of doses are administered in a hospital setting, and considered the initial dose of zoledronic acid may be administered in hospital. However, the Committee considered zoledronic acid would be more likely to be administered longer-term in the community when compared with pamidronate, given the shortened infusion time. The Committee considered this may be beneficial in improving access to those in rural areas who would currently be required to access a hospital infusion service.

7.24. On balance, the Committee considered that the faster infusion time of zoledronic acid compared to pamidronate offered significant benefit to the healthcare sector and that there were no significant clinical risks in funding zoledronic acid for moderate to severe hypercalcaemia, given pamidronate was already being used for this indication.

7.25. The Committee considered that the below table summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for zoledronic acid if it were to be funded in New Zealand for moderate to severe hypercalcaemia. 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 symptomatic hypercalcaemia
Intervention	Intravenous zoledronic acid 4 mg or 5 mg, administered over 15 minutes and repeated following relapse (approximately every 4-6 weeks)
Comparator(s)	Pamidronate disodium 60-90 mg, administered over 2 hours and repeated following relapse (approximately every 2-4 weeks)
Outcome(s)	Reduction in symptoms of hypercalcaemia
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.	

8. Fluticasone with vilanterol 200/25 mcg – severe asthma

Application

8.1. The Committee reviewed the September 2020 supplier application for fluticasone with vilanterol 200/25 mcg (Breo Ellipta 200) for the treatment of severe asthma.

8.2. The Committee noted that Pharmac had received correspondence from a clinician in response to Pharmac's December 2019 consultation on a proposal to fund mepolizumab, regarding the use of multiple inhalers in order to achieve the inhaled corticosteroid dose required to access biologic asthma treatment and challenges associated with this.

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

Recommendation

8.4. The Committee **recommended** that the application for fluticasone furoate with vilanterol 200/25 mcg for the treatment of severe asthma be **declined.**

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

- the evidence in the target population (patients with uncontrolled severe asthma) was from a single randomised controlled trial that reported no difference between currently funded treatments and the proposed treatment
- there was no identifiable unmet health need that could be addressed by this high-dose inhaled corticosteroid, given currently funded treatments
- funding this product would not be reasonably expected to improve the current inequitable outcomes for Māori and Pacific peoples with severe asthma to any appreciable extent
- there was already a full list of funded inhalers for people with asthma and that the added benefit of this treatment did not warrant the added complexity of funding another inhaler
- there was an increased risk of pneumonia when receiving high dose inhaled corticosteroids and that this dose dependent effect was present with fluticasone furoate as well.

8.6. The Committee considered that Pharmac should seek the Respiratory Subcommittee's review of the Special Authority criteria for mepolizumab and omalizumab in case those agents' Special Authority criteria included a requirement in order to gain access that was inappropriate clinically such as an unnecessarily high inhaled corticosteroid dose.

Discussion

8.7. PTAC and PTAC Subcommittees may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, albeit complementary, roles, expertise, experience, and perspectives.

8.8. The Committee noted that the original August 2014 application for fluticasone furoate with vilanterol (200/25 mg) was reviewed by PTAC in November 2014 and by the Respiratory Subcommittee in September 2015 who each recommended the application be declined and raised concerns around risks associated with high doses of inhaled steroids and high doses of fluticasone furoate in particular.

8.9. The Committee noted that in September 2020, the supplier (GlaxoSmithKline) submitted a new application for fluticasone furoate with vilanterol (200/25), in light of the December 2019 Pharmac proposal to decline funding the high-dose fluticasone propionate with salmeterol application. The Committee noted that the new application was reviewed by the Respiratory Subcommittee in October 2020, which recommended funding fluticasone furoate/vilanterol 200/25 mcg (Breo Ellipta 200) for severe asthma with a medium priority within the context of respiratory disease, due to the health need of this patient group and the potential benefits of fluticasone furoate/vilanterol 200/25 mcg, whilst noting the risks associated with use of high dose inhaled corticosteroids in this patient group.

8.10. The Committee noted that PTAC reviewed the record of the October 2020 Respiratory Subcommittee in February 2021 and PTAC had considered that it should review the application for fluticasone furoate/vilanterol 200/25 mcg (Breo Ellipta 200) for the treatment of severe asthma with a focus on adverse events and risks; the patient population, treatment paradigm and Special Authority criteria; and costs and savings.

8.11. The Committee noted the September 2020 application was for high-dose fluticasone furoate with vilanterol (200/25 mg) as a dry powder device (Breo Ellipta 200), which is taken once daily and is reported to be a potent inhaled corticosteroid with a high affinity for the glucocorticoid receptor with a long duration of action and low systemic absorption.

8.12. The Committee noted that the New Zealand asthma guidelines for adolescents and adults describe a comprehensive treatment paradigm with steps based on consultation, assessments and management which may include pharmacological treatments (Beasley et al. N Z Med J. 2020;133:73-99). The Committee noted that there is a substantial range of funded inhaled treatments such as short-acting beta agonists (SABA), inhaled corticosteroids (ICS), long-acting beta2 agonists (LABA) and combination inhaled corticosteroids with long acting beta2 agonists (ICS/LABA) such as fluticasone furoate/vilanterol (FF/VI) 100/25 mcg.

8.13. The Committee noted that the 2020 Global Initiative for Asthma (GINA) guidelines recommend ICS-containing maintenance treatment to reduce the risk of serious exacerbations, preferably with low-dose ICS-formoterol as a reliever, also known as anti-inflammatory reliever (AIR) with or without maintenance therapy. Members considered these regimens are appealing to patients as they can provide acute relief of symptoms, which aligns well with patient desires and behaviour. Alternatively, SABA may be used as a reliever in combination with ICS.

8.14. The Committee considered that the patient population targeted in this application for high-dose fluticasone furoate/vilanterol (FF/VI) 200/25 mcg are those with severe uncontrolled asthma. The Committee noted that the treatment with FF/VI 200/25 mcg is proposed to fit within the asthma treatment paradigm after standard dose treatment with ICS/LABA and SABA (as AIR with or without maintenance therapy) and before use of biologic treatment mepolizumab or omalizumab. The Committee noted that the small group considered by the application have severe asthma could potentially progress to funded biologic treatments.

8.15. The Committee noted that patients with severe asthma that is uncontrolled on other therapies and their clinicians may reduce the risk of severe exacerbations by undergoing treatment with ICS/formoterol maintenance and reliever therapy (MART). The Committee noted that there is evidence from a systematic review and meta-analysis that such treatment is more effective than high dose ICS/LABA plus SABA (Sobieraj et al. JAMA. 2018;319:1485-96), therefore the Committee considered that the comparator treatment in this small group with severe asthma would be AIR plus maintenance therapy.

8.16. The Committee was made aware of a systematic review which reported there was no evidence to suggest that once-daily administration of asthma treatment improves clinically important patient outcomes (Zhang et al. Int J Chron Obstruct Pulmon Dis. 2020; 15: 417–38). The Committee considered that the range of funded asthma treatments can provide higher doses of inhaled corticosteroids in other combinations and therefore no unmet need for a high-dose combined product was identified, although the Committee noted that an additional prescription charge (due to an extra inhaler) may present a barrier for some patients accessing high dose inhaled corticosteroids with currently funded inhalers.

8.17. The Committee considered there to be potential risk of receiving excessively high doses of inhaled corticosteroids with funded products and regimens, as high doses would be received by overuse. The Committee considered that overuse of a higher dose of inhaled corticosteroid would present risks including a greater risk of developing pneumonia. Members noted the supplier-provided data that indicated that the risk of pneumonia associated with FF/VI 200/25 mcg is dose-dependent and may be related to the lung effects of inhaled corticosteroid (not systemic effects), which will be present despite low systemic absorption of fluticasone furoate (Fluticasone furoate/Vilanterol periodic benefit risk evaluation report. GSK. 2015 [unpublished]).

8.18. The Committee noted that there is evidence of greater disease burden and worse asthma outcomes in Māori and Pacific people compared with non-Māori and non-Pacific people (Ministry of Health, 2013/14 New Zealand Health Survey and National Minimum Data Set [NMDS]). The Committee was made aware of evidence that AIR with or without maintenance therapy is well accepted by Māori people with asthma and that it provides good asthma control with low doses of inhaled corticosteroid, although the particular study was not sufficiently powered to detect large differences for these outcomes (Baggot et al. BMJ Open. 2020;10:e037491; Hardy et al. N Z Med J. 2020;133:61-72).

8.19. The Committee noted that the key evidence for this application comes from the randomised, double-blind, phase III CAPTAIN study of FF/VI compared with standard of care treatment options (Lee et al. Lancet Respir Med. 2021;9:69-84) which was described by the Respiratory Subcommittee in October 2020.

8.19.1. The Committee noted that the mean Asthma Control Questionnaire (ACQ)-6 score at screening was 2.51 and that ACQ-7 at randomisation was about 2.12 (on a scale of zero to six); the Committee considered that this patient group had uncontrolled (score >1.5) but mild to moderate asthma symptoms, rather than severe.

8.19.2. The Committee noted that the difference in ACQ-7 responder rate with FF/VI 200/25 mcg compared with FF/VI 100/25 mcg at 24 weeks was not formally statistically significant (odds ratio 1.34, 95% CI: 1.00 to 1.79).

8.19.3. The Committee noted that the primary outcome of forced expiratory volume in one second (FEV1) was assessed at 24 weeks and that the minimal clinically important difference (MCID) in trough FEV1 from baseline was 100 mL based on the literature (Jones et al. Am J Respir Crit Care Med. 2014;189:250-5). The Committee considered that the reported mean change from baseline in clinic trough FEV1 at week 24 of 51 mL (95% CI: 8 to 95) with FF/VI 200/25 mcg vs FF/VI 100/25 mcg did not meet the MCID (Table 13, Supplementary Appendix). The Committee considered that the CAPTAIN results suggest a reduction in annual exacerbation rate, however, it was unclear whether or not this was statistically significant due to wide confidence intervals.

8.19.4. The Committee considered that the treatment-related adverse events and serious adverse events were similar between FF/VI 200/25 mcg and FF/VI 100/25 mcg, and that health-related quality of life data suggested that there was no measurable difference in quality of life between treatment arms in the CAPTAIN study.

8.19.5. The Committee considered that the CAPTAIN study provided high-quality evidence from a single randomised controlled trial that high-dose FF/VI 200/25 mcg does not improve mean trough FEV1 after 24 weeks of treatment and does not improve health-related quality of life compared with FF/VI 100/25 mcg in patients with mild to moderate asthma.

8.20. The Committee noted an open-label, parallel group, randomised (1:1) controlled trial of 4,233 patients who received a once-daily inhaled combination of either 100 mcg or 200 mcg fluticasone furoate with 25 mcg vilanterol or optimised usual care (Woodcock et al. Lancet. 2017;390:2247-55). The Committee noted that 35% of participants who received FF/VI received a 200 mcg dose, although outcomes were not reported by dose. The Committee noted that at week 24, the adjusted mean asthma control test (ACT) score increased by 4.4 points from baseline in patients who received treatment with FF/VI compared with 2.8 points in the usual care group (difference of 1.6 [95% CI 1.3 to 2.0], P<0.0001). The Committee noted that the MCID of 3, was reached in patients who received FF/VI, however, it was not reached in the group that received optimised usual care. However, the Committee noted that the difference between treatments did not indicate a clinically important difference. The Committee considered that this randomised controlled trial provided strong evidence that FF/VI 200/25 mcg offers no clinically meaningful benefit above optimised usual care in this trial population.

8.21. The Committee noted a phase IIIb open-label, prospective randomised controlled trial of FF/VI (either high dose or standard dose) compared with ICS/LABA with SABA which included 423 patients with uncontrolled severe asthma (Devillier et al. Respir Med. 2018;141:111-20). Members noted that the proportion of patients who received the high dose FF/VI was not reported and that the trial outcomes were not reported according to treatment dose. Members noted that a treatment difference in ACT score of 0.8 was reported at week 12, favouring FF/VI, although this was less than the MCID of three and results at all other timepoints did not indicate any differences. Members considered that the trial results suggested non-inferiority of FF/VI compared with standard of care at six, 18 and 24-week timepoints. Members considered that this study included a relevant patient population with uncontrolled severe asthma (and is the only identified study in patients with severe asthma), although patient outcomes and the proportion of patients receiving higher doses of inhaled corticosteroid were unclear.

8.22. The Committee noted that the evidence to support the use of FF/VI 200/25 mcg came from only one randomised controlled trial in the target population (Devillier et al. 2018), as other trials included participants with less severe asthma. The Committee noted that no trials were identified that compared high-dose FF/VI with standard of care inflammatory reliever therapy i.e. budesonide/formoterol AIR with or without maintenance therapy. In addition, the Committee considered that there was high-quality evidence that suggests FF/VI 200/25 mcg is no more effective than standard of care options, such as fluticasone propionate/salmeterol.

8.23. The Committee considered that Pharmac's estimates of about 943 prevalent patients currently taking FF/VI 100/25 mcg or fluticasone/salmeterol 250/25 mcg on top of high dose fluticasone monotherapy was reasonable and that uptake of FF/VI 200/25 mcg, if funded in this population, would be high. The Committee considered that the Breo Ellipta device has a convenient once a day dosing regimen and is easy to use. The Committee considered that, if funded, there would be a risk that FF/VI 200/25 mcg could be used in other indications COPD, leading to the potential for harm from the high-dose corticosteroid and a significant fiscal risk. Members also considered there was a risk if patients take multiple doses as they are used to doing with other inhalers, as they would instead inhale excessive corticosteroid doses.

8.24. Based on evidence from the systematic review that reported no benefit in clinical outcomes with one inhaler compared with two inhalers (Zhang et al. 2020), the Committee considered that FF/VI 200/25 mcg may not improve existing health outcome inequities and would not replace all inhalers in this patient population, as many patients have a salbutamol

inhaler for reliever therapy. The Subcommittee considered that the benefit of funding FF/VI 200/25 would be derived from the reduction from three inhalers to two inhalers for this patient group, potentially resulting in improved compliance. Such a reduction would reduce pharmacy-related direct costs to patients by reducing co-payments from three to two in many cases, which may be significant for some patients.

8.25. Overall, the Committee considered that there was no identifiable unmet health need that could be addressed by the high-dose FF/VI 200/25 mcg product, given that high doses of inhaled corticosteroid can be achieved with combinations of currently funded products. The Committee considered that meaningful outcomes of interest would be ACQ score or exacerbation rate for this patient population.

8.26. The Committee considered that Pharmac should seek the Respiratory Subcommittee's review of the Special Authority criteria for mepolizumab and omalizumab in case the Special Authority criteria for these agents included a requirement that was inappropriate clinically in order to gain access such as an unnecessarily high inhaled corticosteroid dose.

9. Risankizumab for chronic plaque psoriasis (1st and 2nd line)

9.1. .

Marius Rademaker reported that:

- He is a NZ Principal Investigator for 3 clinical trials on upadacitinib (a JAK inhibitor) for severe atopic dermatitis, sponsored by AbbVie through Clinical Trial NZ. The Chair deemed this as a potential conflict and determined Marius would participate in the discussion but not vote on the risankizumab proposal.
- He is a member of the Australasian Medical Dermatology Group who have received unrestricted grants over several years to cover meeting travel expenses from AbbVie. Marius would participate in the discussion but not vote on the risankizumab proposal.
- He was a co-investigator of a published quality of life study of adalimumab in psoriasis/rheumatoid arthritis/inflammatory bowel disease sponsored by AbbVie with no personal payment received. The Chair deemed this was not a conflict.
- He has been a co-investigator in an international quality of life study of moderate/severe atopic eczema, sponsored by AbbVie with no personal payment received. The Chair deemed this was not a conflict.

Application

9.2. The Committee reviewed the application for risankizumab in the treatment of chronic plaque psoriasis (1st and 2nd line biologic treatment).

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

Recommendation

9.4. The Committee **recommended** that risankizumab for the first line treatment of chronic plaque psoriasis be listed with a **medium priority** subject to the following Special Authority criteria:

> **Initial application – (severe chronic plaque psoriasis, first or subsequent line biologic)** only from a dermatologist. Approvals valid for 4 months for applications meeting the following criteria:
> All of the following:
> Either:
> 1 Both:
> 1.1 The patient has had an initial Special Authority approval for adalimumab, etanercept or secukinumab, or has trialled infliximab in accordance with the General Rules of the Pharmaceutical Schedule, for severe chronic plaque psoriasis; and
> 1.2 Either:

1.2.1 Patient has experienced intolerable side effects from adalimumab, etanercept, infliximab or secukinumab; or
1.2.2 Patient has received insufficient benefit from adalimumab, etanercept, infliximab or secukinumab; or

2 All of the following:

2.1: Either:

2.1.1 Patient has "whole body" severe chronic plaque psoriasis with a Psoriasis Area and Severity Index (PASI) score of greater than 10, where lesions have been present for at least 6 months from the time of initial diagnosis; or
2.1.2 Patient has severe chronic plaque psoriasis of the face, or palm of a hand or sole of a foot, or genital or flexural psoriasis present for at least 6 months from the time of initial diagnosis; and

2.2 Patient has tried, but had an inadequate response* to, or has experienced intolerable side effects from, at least three of the following (at maximum tolerated doses unless contraindicated): phototherapy, methotrexate, ciclosporin, or acitretin; and
2.3 A PASI assessment or Dermatology Life Quality Index (DLQI) assessment has been completed for at least the most recent prior treatment course, preferably while still on treatment but no longer than 1 month following cessation of each prior treatment course; and
2.4 The most recent PASI or DLQI assessment is no more than 1 month old at the time of application.

*A treatment course is defined as a minimum of 12 weeks of treatment. "Inadequate response" is defined as: for whole body severe chronic plaque psoriasis, a PASI score of greater than 10, as assessed preferably while still on treatment but no longer than 1 month following cessation of the most recent prior treatment; for severe chronic plaque psoriasis of the face, hand or foot, or genital or flexural psoriasis, at least 2 of the 3 PASI symptom sub scores for erythema, thickness and scaling are rated as severe or very severe, and the skin area affected is 30% or more of the face, palm of a hand or sole of a foot, as assessed preferably while still on treatment but no longer than 1 month following cessation of the most recent prior treatment.

Renewal – (severe chronic plaque psoriasis) only from a dermatologist or practitioner on the recommendation of a dermatologist. Approvals valid for 6 months for applications meeting the following criteria:
Both:
1. Either:

1.1 Patient's PASI score has reduced by 75% or more (PASI 75) as compared to baseline PASI prior to commencing risankizumab; or
1.2 Patient has a Dermatology Life Quality Index (DLQI) improvement of 5 or more, as compared to baseline DLQI prior to commencing risankizumab; and

2. Risankizumab is to be administered at a maximum dose of 150 mg every 12 weeks

9.5. The Committee **recommended** that risankizumab for the second line treatment of chronic plaque psoriasis be listed with a **high priority** subject to the following Special Authority criteria:

Initial application – (severe chronic plaque psoriasis, second line biologic) only from a dermatologist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:
1 The patient has had an initial Special Authority approval for adalimumab, etanercept or secukinumab, or has trialled infliximab in accordance with the General Rules of the Pharmaceutical Schedule, for severe chronic plaque psoriasis; and
2 Either:

2.1 Patient has experienced intolerable side effects from adalimumab, etanercept, infliximab or secukinumab; or
2.2 Patient has received insufficient benefit from adalimumab, etanercept, infliximab or secukinumab; and

3 A PASI assessment or Dermatology Life Quality Index (DLQI) assessment has been completed for at least the most recent prior treatment course, preferably while still on treatment but no longer than 1 month following cessation of each prior treatment course; and
4 The most recent PASI or DLQI assessment is no more than 1 month old at the time of application.

Renewal – (severe chronic plaque psoriasis) only from a dermatologist or practitioner on the recommendation of a dermatologist. Approvals valid for 6 months for applications meeting the following criteria:
Both:
1. Either:

1.1 Patient's PASI score has reduced by 75% of more (PASI 75) as compared to baseline PASI prior to commencing risankizumab; or

1.2 Patient has a Dermatology Life Quality Index (DLQI) improvement of 5 or more, as compared to baseline DLQI prior to commencing risankizumab; and
2. Risankizumab is to be administered at a maximum dose of 150 mg every 12 weeks,

9.6. In making these recommendations, the Committee noted the high health need of patients with chronic plaque psoriasis and their whānau, the superior efficacy of risankizumab compared to currently funded treatments, and also took into account the lack of long-term follow-up data meaning there is little or no information pertaining to development of antibodies to risankizumab, and the durability of clinical effect, the lack of long-term safety data, and the lack of an appropriate treatment algorithm upon drug failure. The Committee also considered the benefit of funding a biologic with an alternative mechanism of action compared to current treatments, other than an anti-TNF or anti -IL-17 biologic, and the potential to compete the market.

Discussion

9.7. The Committee noted that this application had previously been reviewed by the Dermatology Subcommittee in November 2020, where risankizumab received a high recommendation for both first- and second-line treatment chronic plaque psoriasis. The Committee noted that it requested to review the application following the Dermatology Subcommittee, noting that PTAC had not considered risankizumab previously for any indications and it is a new biologic agent with a different mechanism of action to biologic agents previously considered. The Committee noted at the time that there was a potentially significant patient pool, and clearer advice on patient numbers, cost, and data on quality adjusted life years could be provided.

9.8. The Committee noted that psoriasis is a chronic immune-mediated disease, which is characterised by thickening of the epidermis, heavy inflammatory infiltrate, and vascular changes, and that plaque psoriasis accounts for 80% of psoriasis diagnoses. The Committee also noted that psoriasis has been described by the World Health Organization (WHO) as a chronic, painful, disfiguring, and disabling disease for which there is no cure and with significant impairment in quality of life, and that the WHO has recognised psoriasis as a serious noncommunicable disease, highlighting that many people in the world suffer needlessly from psoriasis due to delayed diagnosis, inadequate treatment options, insufficient access to care, and because of social stigmatisation.

9.9. The Committee noted that severe chronic plaque psoriasis is defined as having a psoriasis area and severity index (PASI) score of >10 and/or a Dermatology Life Quality Index (DLQI) score of >10. The Committee was made aware of an indirect systematic review that compared quality of life in psoriasis with other chronic diseases using EQ-5D-derived utility values and reported the mean EQ-5D index scores for psoriasis (all severities) ranged from 0.52 (similar to that of end-stage renal disease or visual disorders) to 0.9 (similar to cardiovascular and cancer diseases; Møller. Patient Relat Outcome Meas. 2015;6:167-77). The Committee was made aware of a systematic review and meta-analysis of health state utility value calculated from EQ-5D-3L and EQ-5D-5L for psoriasis as a general condition, for plaque psoriasis, and for psoriatic arthritis (the values being 0.748 (0.718, 0.777; 98.8%), 0.755 (0.727, 0.783; 98.6%), and 0.585 (0.538, 0.632; 98.2%), respectively; Yang Z, et al. J Dermatolog Treat. 2020;1-8).

9.10. The Committee noted the appropriate metric for PASI treatment outcomes had changed since the Committee last considered a psoriasis systemic agent and wanted clear supporting evidence for the health utilities for this patient group, likely patient numbers, and supporting evidence for these factors.

9.11. The Committee was made aware of a cross-sectional analysis on the relationship between quality of life and severity of psoriasis, assessed using data from UltIMMa-1 and UltIMMa-2 studies (Strober et al. BMJ Open. 2019;9:e027535). The Committee noted that the more severe the psoriasis, the worse the symptoms; DLQI scores increased ($p<0.05$), EuroQoL Visual Analogue Scale (EQ-VAS) decreased ($p<0.05$) and Work Productivity and Activity Impairment (WPAI) scores increased regardless of body surface area affected. The Committee noted that by body surface area score, moderate to very severe psoriasis was

associated with poorer outcomes for the 'impairment while working' and 'daily activities impaired' WPAI domains (all p<0.05 vs mild psoriasis), and very severe psoriasis was associated with increased 'work hours missed' and 'work hours affected' (both p<0.05 vs mild psoriasis.

9.12. The Committee was made aware of a study of how family and whānau caring for patients with psoriasis are affected (Martínez-García. J Am Acad Dermatol. 2014;71:302-7). The Committee noted that the presence of psoriasis impaired the quality of life of 87.8% of cohabitants; Family Dermatology Life Quality Index (FDLQI) scores were significantly associated with DLQI scores of patients (correlation coefficient = 0.554; P<001). The Committee also noted that anxiety and depression levels did not differ between patients and family but were significantly higher than control patients and their families (P<001).

9.13. The Committee noted that currently patients with moderate to severe chronic plaque psoriasis are treated with phototherapy, acitretin, methotrexate and/or ciclosporin and that under current Special Authority access criteria, patients must have tried, but had an inadequate response to, be contraindicated to, or experienced intolerable side effects from, at least three of these treatments, prior to biologic treatment. The Committee also noted that both methotrexate and ciclosporin are currently funded without restriction, while acitretin has Special Authority restrictions in place.

9.14. The Committee noted that adalimumab, etanercept, infliximab and secukinumab are the currently funded biologics for severe chronic plaque psoriasis, subject to restrictions. The Committee noted that adalimumab, etanercept and infliximab are anti TNF-α therapies, while secukinumab is an anti-interleukin-17 (IL-17) therapy. The Committee noted that anti-IL-12/23 therapies can also be used as biologic treatment for psoriasis, but that there are currently no funded options in New Zealand. The Committee considered there would be benefit in funding another anti-IL biologic and considered the potential for a competitive process to fund another biologic treatment line for psoriasis.

9.15. The Committee was made aware of a clinical review of the evidence for adalimumab in the treatment of plaque psoriasis conducted by the Canadian Agency for Drugs and Technologies in Health (CADTH; Peprah & Aragez. Canadian Agency for Drugs and Technologies in Health; 2020). The Committee noted that the CADTH considered that there was consistent evidence that adalimumab was less effective than infliximab, ixekizumab, risankizumab, and secukinumab in achieving skin clearance and improvements in health-related quality of life in patients diagnosed with moderate-to-severe psoriasis.

9.16. The Committee noted that the treatment landscape for psoriasis has changed markedly in recent years and considered that this was likely influenced by marketing strategies for new biologics by pharmaceutical companies. The Committee considered that one such change is the treatment target of PASI 75 to PASI 90 and considered that this will eventually move to PASI 100.

9.16.1. The Committee was made aware of the PSO-BIO-REAL study, a non-interventional observational study that reported, in a real-world setting of 836 patients treated with biologic therapy, that there were marked differences in patient reported outcomes for stinging, flaking, pain, itching, burning, redness, and cracking skin when psoriasis response improved from PASI 75 to PASI 90 and then PASI 100 (Lacour et al. Dermatol Ther (Heidelb). 2020;10:1099-109).

9.16.2. The Committee also was made aware of a systematic review of 66 studies investigating PASI 100 response and noted that PASI 100 was more likely to be achieved with biologic treatments compared to methotrexate. The Committee noted that IL-17 inhibitors achieved 41.4% to 67.5% PASI 100 response at 1 year, and IL-12/23 treatment achieved PASI 100 in 41.8%/56.3% at 1 year (Romero et al. J Dermatolog Treat. 2021;1-9), although this comparison was indirect.

9.17. The Committee was made aware of a supplier-funded systematic review and meta-analysis assessing whether greater improvement in PASI scores from PASI 75-89 to PASI 90 is associated with greater quality of life improvements, specifically DLQI scores (Puig et al. J Eur Acad Dermatol Venereol. 2017;31:213-20). The Committee noted that the change from baseline in DLQI was 78% in PASI 75–89 responders (95%CI 75% to 82%) and was 90% for PASI 90 responders (95% CI 88% to 93%), implying perhaps a 12% greater improvement in DLQI score for PASI 90 compared with PASI 75–89. The Committee noted that the same meta-analysis also reported a clinically significant difference in DLQI score of 0/1 between PASI 75-89 and PASI 90 responders (45%, 95% CI 41.05 to 50.0% vs 73%, 95% CI 70.0% to 76.0%, respectively, P<0.0001). The Committee noted the meta-analysis used different trials, settings and treatments across the PASI metrics, but considered PASI 90 to be clinically meaningfully better than PASI 75.

9.18. The Committee noted that risankizumab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds with high affinity to the p19 subunit of human interleukin 23 (IL-23) cytokine and inhibits its interaction with the IL-23 receptor complex, which inhibits IL-23-dependent cell signalling and release of pro-inflammatory cytokines.

9.19. The Committee noted that there are over 25 indirect comparison network meta-analyses for treatments for chronic plaque psoriasis, including a Cochrane living systematic review (Sbidian et al. Cochrane Database Syst Rev. 2021;4:CD011535) which reported risankizumab as the third best treatment for chronic plaque psoriasis, behind infliximab (funded in New Zealand) and ixekizumab (an IL-17 inhibitor not funded in New Zealand).

9.20. The Committee noted that there have been several head-to-head direct comparator studies comparing risankizumab with adalimumab, ustekinumb, secukinumab, or placebo:

- Reich et al. Lancet. 2019;394:576-86: The randomised, double-blind, active-comparator-controlled IMMvent phase III trial comparing risankizumab with adalimumab in patients with moderate-to-severe plaque psoriasis. At week 16, PASI90 was achieved in 218 (72%) of 301 patients given risankizumab and 144 (47%) of 304 patients given adalimumab (adjusted absolute difference 24.9% [95% CI 17.5-32.4%]; p<0·0001).
- Gordon et al. Lancet. 2018;392:650-61: Results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials (UltIMMa-1 and UltIMMa-2) assessing the efficacy and safety of risankizumab compared with placebo or ustekinumab in patients with moderate-to-severe chronic plaque psoriasis. PASI90 at week 16 in the UltIMMa-1 trial reported an adjusted difference of 33.5% between risankizumab and ustekinumb (95% CI 22.7 to 44.3, p<0.0001), and a 70.3% adjusted difference between risankizumab and placebo (95% CI 64.0 to 76.7, p<0.0001) PASI90 at week 16 for UltIMMa-2 reported an adjusted difference between risankizumab and ustekinumab of 27.6% (95% CI16.7 to 38.5, p<0.0001), and an adjusted difference of 72.5% (95% CI 66.8 to 78.2) for risankizumab compared to placebo.
- Blauvelt et al. JAMA Dermatol. 2020;156:649-58: The withdrawal trial of efficacy and safety of continuous risankizumab versus treatment withdrawal in patients with moderate to severe plaque psoriasis (IMMhance trial). At week 16, PASI90 was achieved in 73.2% of patients receiving risankizumab versus 2.0% of patients on placebo (adjusted risk difference 70.8%; 95% CI 65.7%-76.0%; P <0.001).
- Warren et al. Br J Dermatol. 2021;184:50-9: a randomised, open-label, efficacy-assessor-blinded phase III clinical trial assessing the efficacy and safety of risankizumab versus secukinumab in patients with moderate-to-severe plaque psoriasis. Risankizumab was noninferior to secukinumab in the proportion of patients achieving PASI90 at week 16 (73·8% vs. 65·6%; difference of 8·2%, 96·25% CI -2·2 to 18·6) and superior to secukinumab at week 52 (86·6% vs. 57·1%; difference of 29·8%, 95% CI 20·8 to 38·8; P < 0·001.

9.21. The Committee was made aware of a systematic review of 25 indirect comparison network meta-analyses of at least two biologics for moderate-to-severe psoriasis (Wright et al. 2021). The Committee noted that IL-17 inhibitors (brodalumab, ixekizumab,

secukinumab), IL-23 inhibitors (guselkumab and risankizumab), and infliximab were reported as being the most efficacious biologic treatments.

9.22. The Committee was made aware of an indirect comparison network meta-analysis for the comparison of efficacy and safety of IL-23 targeted drugs (ustekinumab, guselkumab, tildrakizumab, and risankizumab in the treatment of moderate to severe psoriasis (Shi et al. Dermatol Ther. 2020;33:e13802). The Committee noted that 90 and 180 mg risankizumab were reported to be more effective than tildrakizumab (5, 25, 100, and 200 mg), ustekinumab (45 mg, 90 mg, body weight-based administration), guselkumab 100 mg and risankizumab at doses of 75 and 150 mg. The Committee noted that 90 mg risankizumab has the best efficacy index for PASI75, while 180 mg risankizumab ranked first in PASI90. The Committee also noted that there was no significant difference in the risk of adverse events between drugs targeting IL-23 and placebo.

9.23. The Committee was made aware of an additional indirect comparison network meta-analysis of 71 randomised controlled trials of the short-term and long-term comparative efficacy of biologic and oral treatments for moderate-to-severe psoriasis (Armstrong et al. Dermatol Ther (Heidelb); 2021; online ahead of print). The Committee noted that the PASI 90 response rates were highest for ixekizumab, risankizumab, and brodalumab, which were significantly higher than those for guselkumab, secukinumab, infliximab, certolizumab, ustekinumab, adalimumab, tildrakizumab, etanercept, apremilast, and dimethyl fumarate. The Committee also noted that The PASI 100 response rates were highest for ixekizumab (41.4%), risankizumab (40.8%), and brodalumab (40.3%).

9.24. In considering the above network meta-analyses of efficacy, the Committee both reiterated and emphasised what it considered to be the inherent limitations and lesser quality of such indirect comparison methods generically, when compared with direct comparisons.

9.25. The Committee considered that the evidence for risankizumab for the treatment of moderate to severe chronic plaque psoriasis to be of high strength and quality. The Committee also considered that the evidence suggests that risankizumab has similar or higher efficacy to other biologic treatments, is substantially better at achieving a PASI90 score than adalimumab and is incrementally superior to secukinumab in achieving a PASI90, especially when compared directly in the several head-to-head RCTs noted earlier.

9.26. The Committee note that risankizumab is formulated in a pre-filled syringe for subcutaneous injection and could therefore be dispensed in the community for self-administration at home. The Committee noted that risankizumab is administered at week 0 and 4 and every 12 weeks thereafter for maintenance, which the Committee considered to be a more suitable dosing schedule than other biologic treatments: 52 injections a year with etanercept, 26 per year with adalimumab, 12 per year with secukinumab, and 7 infusions per year for infliximab. The Committee also noted that there are significant access issues with infliximab given it is administered as an infusion. The Committee highlighted this is exacerbated in dermatological indications as many patients receive care from private specialists who do not have the infusion facilities to administer infliximab.

9.27. The Committee noted that there are limited data on the long-term effectiveness of risankizumab, and that it is unclear if prior treatment with risankizumab would influence the efficacy of biologics in a later line of treatment ~~if~~ should risankizumab fail. The Committee considered that if risankizumab were to be funded, it may be more beneficial as a second-line treatment as there is proven efficacy of risankizumab following other biologics, but limited evidence for the inverse scenario. The Committee considered that it would be clinically useful to have a biologic with a different mechanism of action to the currently funded treatment options, so that clinicians have a broader range of treatment options.

9.28. The Committee noted that in an assessment from Japan, risankizumab was expected to provide 0.30–0.89 additional QALYs versus comparator biologics, and based on typical willingness-to-pay benchmarks for Japan was considered cost-effective versus other biologics (Saeki et al. J Dermatolog Treat. 2020;1-11). The Committee considered that

market dynamics and potential uptake of risankizumab are difficult to predict without more information regarding long-term drug efficacy and if the efficacy of other biologics changes if given after treatment with risankizumab. The Committee considered it reasonable to assume that the efficacy of adalimumab after risankizumab failure is likely to be lower than the efficacy of adalimumab in a first-line setting.

9.29. The Committee considered that risankizumab may not be the first-choice agent in psoriasis patients who have significant psoriatic arthritis (approximately 15%), as there is limited evidence demonstrating the benefit of risankizumab in arthritis. The Committee considered this may change as evidence for risankizumab in this setting evolves.

9.30. The Committee considered that if risankizumab were to be funded as only a second-line option, that between 35 and 50% of biologic eligible patients over 4-5 years would switch to risankizumab following failure of first-line biologic treatment, usually with adalimumab or secukinumab. The Committee also considered that, if risankizumab were to be funded for any line of treatment, 25-40% of new biologic eligible patients would use risankizumab as 1st line biologic, and a total of 50% of biologic eligible patients would be using risankizumab, regardless of treatment line, after four or five years.

9.31. The Committee considered that a small number of patients who experience primary treatment failure require hospitalisation, which may be as long as three weeks. The Committee considered infliximab is also used in some cases of treatment failure, and that risankizumab could reduce hospitalisation and infliximab use, which would be of benefit to the health system.

9.32. The Committee considered that adalimumab and secukinumab are the most commonly administered first-line biologics in psoriasis. The Committee considered that UV light therapy would not be an appropriate comparator, due to lower PASI 75 responses, as well as the potential damage to the skin and it being a very time intensive treatment which would not be suitable for many patients.

9.33. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for risankizumab if it were to be funded in New Zealand for chronic and severe plaque psoriasis. 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 severe chronic plaque psoriasis intolerant, contraindicated or with inadequate benefit from prior systemic therapy and/or biologic therapy
Intervention	Risankizumab 150mg q12w In case of risankizumab failure, adalimumab or secukinumab used second-line therapy
Comparator(s) (NZ context)	Adalimumab 40mg q2w or Secukinumab 300 mg q month In case of adalimumab and secukinumab failure, infliximab ± hospitalisation
Outcome(s)	Greater rates of PASI 75 / 90 / 100 response, increased wellbeing of family and whānau, reduction in hospitalisations
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. Copper chloride and selenium supplementation for patients admitted to hospital with major burns.

Application

10.1. The Committee reviewed the combined application from the National Burns Unit at Middlemore Hospital for copper chloride and selenium supplementation in the treatment of patients hospitalised with major burns.

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

Recommendation

10.3. The Committee recommended that copper chloride and selenium be funded for patients hospitalised with moderate to severe burns with a medium priority subject to the following eligibility criteria:

> Initial application from any relevant practitioner on the recommendation of a National Burns Unit specialist. Approvals valid for 3 months.

10.4. In making this recommendation, the Committee noted:

- the high health need of patients admitted to hospital with major burns
- the strong biological plausibility for the role of trace supplementation in wound healing in the absence of high-quality empirical evidence
- the lack of effective funded alternatives.

Discussion

10.5. The Committee noted the applications for copper chloride and selenium supplementation for patients hospitalised with burns from a pharmacist on behalf of the National Burns Centre based at Middlemore Hospital.

10.6. The Committee noted that it is standard practice internationally and at the National Burns Centre to provide additional copper, selenium and zinc supplementation (already listed on the hospital medicines list) to patients admitted with severe burns. The Committee noted that the National Burns Centre currently accesses copper and selenium through the DHB hospital rapid NPPA assessment process' emergency use rule, and considered that any decision to list copper chloride and selenium in the Pharmaceutical Schedule would likely have only a small impact on the overall use of these products.

10.7. The Committee noted that copper and selenium are critical trace elements in several cellular pathways in growth and metabolism, including those involved in wound healing, and are disproportionately lost in patients with major burns. The Committee noted that there is a strong biological rationale for the role of trace element supplementation in improving skin graft success and in reducing the risk of infection following severe burns.

10.8. The Committee noted that multivitamin and mineral supplements are already listed on the Pharmaceutical Schedule for patients hospitalised with burns. However, the Subcommittee considered that the funded supplements contained levels of copper and selenium that were significantly below the levels required for repletion and improved wound healing in severe cases.

10.9. The Committee noted two publications (Toppi et al. Burns. 2019;45:1456-61 and McInnes et al. Burns. 2019;45:1553-61) from the Burns Registry of Australia and New Zealand (BRANZ), which indicated that there are approximately 18 major burns patients admitted to hospital per year in New Zealand, almost all of which would transferred to the National Burns Centre at Middlemore Hospital for treatment. The Committee noted that most patients admitted to hospital with severe burns were aged between 18 and 40 years of age, and the majority were male.

10.10. The Committee noted the very high health need of patients with major burns, noting a mortality rate of 17% and a median length of stay in intensive care of approximately one week. The Committee noted that the median length of stay in hospital based on ACC data (Toppi et al. 2019) was 24 days.

10.11. The Committee noted a retrospective review of the medical records of patients admitted acutely to hospital in New Zealand with a burn between 1996 and 2006 (Mistry et al. Burns. 2010;36:403-8), which reported higher rates of hospital admission for Māori, Pacific and socioeconomically deprived populations. The Committee noted that these populations were more likely to be exposed to burn hazards such as poor housing quality, lack of smoke detectors, and cigarette smoking.

10.12. The Committee noted that the treatment of patients with major burns required significant hospital resource, noting that approximately 60% of the total cost of hospitalisation was related to inpatient care, followed by operations (20%) and outpatient visits (Koljonen et el. J Burn Care Res. 2013;34:318–25).

10.13. The Committee considered that there is strong biological plausibility for supplementation to be initiated as soon as possible following hospital admission when acute trace element depletion is likely to occur due to significant exudative losses and metabolic and oxidative stress. The Committee noted that supplementation should be continued until the wound has healed and/or any mineral deficiencies are restored. The Committee noted that copper needs to be delivered intravenously due to the competition between copper and zinc for intestinal absorption via the metallothionein transporter.

10.14. The Committee noted two international guidelines that outline the nutritional requirements for patients admitted to hospital with major burns:

10.15. The Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN) (McCalve et al. JPEN J Parenter Enteral Nutr. 2016;40:159-211), which considered the evidence for all antioxidants and for all critically ill patients in the United States

10.16. The European Society for Clinical Nutrition and Metabolism (ESPEN) endorsed recommendations for nutritional therapy in major burns (Rousseau et al. Clin Nutr. 2013;32:497-502). The Committee noted that the ESPEN-endorsed recommendations outline that initiating supplementation immediately after admission is associated with a reduction in lipid peroxidation, improved antioxidant defences, improved immunity with lower

incidence of infectious complications, improved wound healing, and possibly shorter ICU stays.

10.17. The Committee noted that the guidelines noted above are a combination of syntheses of published empirical evidence and expert opinion. While the Committee considered there to be a consensus view that trace element supplementation be included as a part of a broader nutritional strategy for major burn patients, it considered the evidence-base underpinning the guidelines to be limited and of low quality.

10.18. The Members noted that two small prospective, randomised, placebo-controlled trials previously reviewed by PTAC in March 2014 (Berger et al. Am J Clin Nutr.2007;85:1293-1300 & 1301-6) were referenced extensively throughout the ESPEN-endorsed recommendations. The Committee noted that these trials examined the effect of supplementation with copper, selenium and zinc on various parameters of burn healing in patients with burns greater than 20% of body surface area. The Committee noted that trace element supplementation was associated with early normalisation of plasma trace element concentrations, lower grafting requirements, and fewer pulmonary infections, but considered that the trials lacked primary endpoints, power calculations and clarity around the number of participants included in these studies.

10.19. The Committee noted three further publications, which it had not previously reviewed:

- Pantet et al. Clin Nutr. 2019;38:246-51: a retrospective dose-finding study assessing the safety and efficacy of a trace element repletion strategy in 139 patients with burns greater than 20% of body surface area. The Committee considered there to be no significant safety issues in this study associated with doses in line with those outlined by the National Burns Centre (400mg Copper chloride and 300µg Selenium) and noted that the mean number of infections per patient during the first 21 days significantly reduced as higher elemental doses were prescribed, from 2.3 infections per patient to 1.7 infections per patients ($p < 0.05$).
- Berger et al. Crit Care. 2006;10:153: an aggregation of two consecutive, randomised, double-blinded supplementation studies assessing the impact of trace element supplementation on infection risk, wound healing and length of ICU stay in 41 severe burn patients admitted to hospital. The Committee noted that the publication reported no statistically significant reduction in the median length of mechanical ventilation in the supplemented group, however, found a small reduction in the number of total infections (from 2.0 ± 1.0 in the supplement group vs 3.5 ± 1.2 placebo group ($p <0.001$)) and median length of ICU stays as proportion of burned body surface area (0.63 (0.23 to 1.64) supplemented group vs 0.99 (0.43 to 2.48) placebo group ($p = 0.002$)). The Committee considered that while the combined studies reported a meaningful reduction in wound healing, there was insufficient evidence to suggest this translated into shorter hospital stays.
- Kurmis et al. J Burn Care Res. 2016;37:143-59: a systematic review and meta-analysis on trace element supplementation following severe burn injury, which included eight studies. The Committee noted that the analysis reported a significant decrease in infectious episodes with trace element supplementation (weighted mean difference: −1.25, 95% CI −1.70 to −0.80, $p <0.00001$,) but that there was no statistically significant difference in overall mortality (risk ratio 0.96, 95% CI 0.18 t0 5.01, $p =0.96$) or time in intensive care. Of note these findings relied on the Berger studies above and two earlier studies from the same group.

10.20. The Committee noted that, while much of the external validity of the evidence-base is limited by the fact that it is underpinned by a few trials conducted on a small cohort of Swiss patients (the Berger et al. 2006 and 2007 publications), it considered there to be no reason that it would not be relevant to the New Zealand context.

10.21. The Committee considered that empirical evidence supporting trace element supplementation in the setting of major burns to be of moderate strength but low quality,

despite there being a strong mechanistic rationale for their use. The Committee considered that while there was some improvement in endpoints such as the rate of wound healing and the number of infections, there was limited information on the effect on long-term quality of life. Members considered that it was very difficult to establish an evidence-base in this field, particularly regarding longer term health outcomes, noting that BRANZ was set up for this purpose but has experienced low participation rates, high-loss to follow-up and strong responder bias (Gabbe et al. Burn. 2015;41:1732-40).

10.22. The Committee considered it appropriate to limit use to specialist burns units or after consultation with the national specialist burns unit so as to reduce the risk of use outside of the intended patient population. The Committee considered that the existing eligibility criteria for multivitamin and mineral supplements be amended for consistency. The Committee considered that requiring evidence of nutritional deficiency could be introduced if hospital usage is significantly higher than expected.

10.23. The Committee considered the financial risk of funding copper and selenium for this indication to be relatively small, given that trace element supplementation is already used in this setting. Members noted that there is currently limited visibility of hospital usage due to variable reporting and considered that funding via the Pharmaceutical Schedule would improve visibility and that this could be used to tighten restrictions if required. The Committee considered that burns specialists could inform the resource use associated with treating this patient population, and how hospital day and regrafting requirements could be affected by the funding of trace mineral supplementation.

10.24. The Committee considered that it was unclear how many patients may access treatment if trace element supplementation was funded. The Committee considered that Toppi et al. 2019 reported fewer than 20 patients a year, but that this was only adults with severe burns, while Mistry et al. 2010 reflected all patients admitted with burns and was likely an overestimate. The Committee recommended that Pharmac staff engage with burns experts to get a better estimate of current usage.

10.25. The Committee considered that the evidence for trace element supplementation is zinc/selenium/copper in combination, and that this would reflect current practice.

10.26. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for copper and selenium if it were to be funded in New Zealand for the treatment for major burns. 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. The Committee considered the PICO (population, intervention, control, and outcomes) table below to be appropriate, noting that if Pharmac were to revise the eligibility criteria that the population should amended to reflect this. 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 severe burns hospitalised in a specialist burns unit
Intervention	*Selenium drops:* 300 micrograms once daily for duration of hospital admission (median length of stay ~24 days) *Copper chloride:* 4 mg injection daily for up to 30 days; average duration of treatment estimated to be approximately 14 days. Both selenium and copper chloride to be used in combination with funded multivitamins
Comparator(s) (NZ context)	Funded multivitamin and mineral supplements
Outcome(s)	Improvement in midpoint markers e.g. wound healing, reduction in infections
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

11. Emicizumab for Haemophilia A without FVIII inhibitors

Application

11.1. The Committee reviewed the supplier application from Roche for emicizumab for patients with severe haemophilia A without FVIII inhibitors.

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 emicizumab for the treatment of haemophilia A without FVIII inhibitors be funded with a **high priority** subject to the following Special Authority criteria:

> **Initial application – (Haemophilia A without inhibitors)** only from a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has severe congenital haemophilia A (endogenous factor VIII activity ≤1%)
> 2. Emicizumab is to be administered prophylactically at a loading dose of 3 mg/kg once a week for the first 4 weeks, followed by a maintenance dose of 1.5 mg/kg once a week (or the equivalent dosing schedule as per approved Medsafe Data Sheet).
>
> **Renewal – (Haemophilia A without inhibitors)** only from a haematologist. Approvals valid for 12 months for applications meeting the following criteria:
> 1. The treatment remains appropriate and the patient is benefiting from treatment.

11.4. In making this recommendation, the Committee considered:

- the high health need of patients with severe haemophilia A without inhibitors
- the suitability of emicizumab treatment compared with FVIII prophylaxis
- the evidence of benefits from emicizumab for patients and family/whānau from a reduction in annualised bleeding rates and the potential to delay and/or reduce lifetime damage as a result from commencing treatment with emicizumab prophylaxis at a young age
- the health system benefits including hospital savings due to reduction in bleeding events
- the very high cost of emicizumab prophylaxis and ongoing requirement for some FVIII usage to manage bleeding events and surgery, as well as the high cost of current FVIII prophylaxis.

Discussion

11.5. The Committee noted that the epidemiology of haemophilia A has been previously discussed by the Haematology Subcommittee in January 2019 and that the incidence of haemophilia A in Māori is similar to the incidence in non-Māori.

11.6. The Committee considered that in clinical practice, patients with severe haemophilia A might be defined by very low levels of FVIII (<1% normal concentration) rather than by a specific number of bleeding events within a prescribed time frame. The Committee considered that there is strong evidence of a high health need in adults and children with severe haemophilia A without inhibitors and their families/whānau due to progressive joint damage, the risk of life-threatening bleeding events such as intracranial haemorrhage, and the effects of both the disease and its management on family life, physical activities and employment.

11.7. The Committee note that emicizumab is a humanised asymmetric bispecific IgG4 antibody which mimics the function of factor VIIIa (FVIIIa) cofactor activity, directly replacing FVIII for effective haemostasis. The Committee noted that emicizumab is approved by Medsafe for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in adult and paediatric patients with haemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors.

11.8. The Committee noted that emicizumab is currently funded (subject to Special Authority criteria) as a prophylactic treatment for patients with severe haemophilia A who have developed FVIII inhibitors. The Committee noted that this new application sought funding for emicizumab prophylaxis for patients with severe haemophilia A who do not have FVIII inhibitors.

11.9. The Committee noted that treatments for haemophilia A can be given on-demand or as prophylaxis and that other funded options can include FVIII replacement therapy, immune tolerance induction (ITI) for those who have developed inhibitors to FVIII, and FVIII bypassing agents factor VIIa (FVIIa, NovoSeven RT) and FVIII inhibitor bypassing fraction [activity] (FEIBA). The Committee noted the high cost and substantial time (≥1 year) required for immune tolerance induction and considered that bleeding events may be treated with a number of agents especially if FVIII deficiency is not an isolated deficiency for a particular patient.

11.10. The Committee noted that current FVIII prophylaxis requires administration via venous access port in a hospital setting (although subsequently may be administered at home for some patients) three times per week. Members considered it reasonable to estimate that adherence to FVIII prophylaxis could be 100% in children and about 80% in adults, as the latter group are better equipped to independently manage the disease and mitigate its consequences, and children would be under close management for ongoing care. The Committee considered that prophylaxis in young, active children with haemophilia A may provide benefits by delaying and/or preventing long-term damage and disability. The Committee noted that many current treatments for haemophilia A require administration and/or monitoring in a hospital setting, which presents access challenges for patients who do not live near tertiary healthcare services.

11.11. The Committee noted recent evidence suggests a growth in FVIII usage in New Zealand in 2020. The Committee considered FVIII usage is dropping internationally, in comparison to NZ trends. The Committee considered it was uncertain what was driving the increasing usage of FVIII in NZ, and whether usage of FVIII is likely to continue to grow at the same rate.

11.12. The Committee noted that emicizumab is administered as a subcutaneous injection once weekly for the first 4 weeks (loading dose) followed by maintenance dosing of either 1.5 mg per kg once weekly, 3 mg per kg every two weeks, or 6 mg per kg every four weeks. The Committee noted pharmacokinetic data that suggests these dosing schedules achieve lower trough concentrations of emicizumab with increased dose and longer dosing intervals, and that mean concentrations were similar, aligning with thrombin generation which indicates

effective haemostasis (Supplementary Figure 1. Callaghan et al. Blood. 2021;137:2231-42). The Committee was made aware of paediatric dosing data that suggests similar concentrations to adults are achieved (Young et al. Blood. 2019;134:2127-38) and noted that the ongoing HAVEN 5 trial (ClinicalTrials.gov Identifier: NCT03315455) would provide further evidence in this area, once published.

11.13. The Committee noted that international recommendations for funding of emicizumab prophylaxis in Australia, Canada, Scotland and England/Wales generally feature consideration of the high cost of the medicine and include restrictions for funding to defined populations or sub-populations, restrictions to certain prescriber types, and requirements for prior approval of funding.

11.14. The Committee noted recent evidence of long-term outcomes with emicizumab prophylaxis for patients with haemophilia A with or without FVIII inhibitors from the open-label, randomised HAVEN 1, 2, 3 and 4 studies (Callaghan et al. Blood. 2021;137:2231-42). The Committee noted that the HAVEN 1 and 2 trials were described by the Haematology Subcommittee in January 2019. The Committee noted that HAVEN 3 (N=152; patients without inhibitors) and HAVEN 4 (N=48, patients with or without FVIII inhibitors) included adults and adolescents aged ≥12 years with haemophilia A who received either emicizumab 1.5 mg/kg weekly or 3.0 mg/kg every two weeks (HAVEN 3) or emicizumab 6.0 mg/kg (HAVEN 4).

11.14.1. The Committee noted there was 90% compliance in reporting bleeds and medications across all four studies (HAVEN 1-4) and that the annualised bleed rate (ABR) for treated bleeds over the entire study period was 1.4 (95% CI: 1.1 to 1.7) and that this decreased over time. Members considered that without treatment, the ABR was approximately 40 in this patient population. The Committee considered that this was strong evidence for a reduction in bleeds with emicizumab prophylaxis.

11.14.2. The Committee noted that during weeks 121 to 144, 99.4% of participants had three or less treated spontaneous bleeds, and 91.8% of participants did not report any treated spontaneous bleeds. The Committee noted that use of FVIII and FVIIa decreased over time.

11.14.3. The Committee considered that the long-term adverse event data from the HAVEN 1-4 trials indicated that emicizumab was well tolerated; that the most common adverse event was nasopharyngitis and that the most common treatment-related adverse event was injection site reaction (occurring in about 25% of participants). The Committee noted that few discontinuations occurred as a result of adverse events, however, three thrombotic microangiopathic (one with fatal rectal haemorrhage) and two thromboembolic events were reported, all of which were associated with activated prothrombin complex concentrate use.

11.14.4. The Committee noted that anti-drug antibodies with neutralising potential were reported in less than 1% of patients who received emicizumab, and noted that current reporting is less than three years duration. The Committee considered that this was encouraging, noting that in other settings where monoclonal antibodies are used, antibodies tend to develop within a relatively short time period.

11.15. The Committee was made aware of evidence from a multi-centre observational study of emicizumab prophylaxis in 93 children with median age of 8.6 years; of the patients who were <12 years of age (66%), the majority did not have inhibitors (N=49). The authors reported that the mean annualised bleed rate for treated bleeds in patients without inhibitors decreased from 1.6 events (95% CI, 0.9 to 2.4) to 0.4 events (95% CI, 0.2 to 0.6) with emicizumab prophylaxis (P=0.0025) (McCary et al. Haemophilia. 2020;26:631-6).

11.16. The Committee noted that the HAVEN 3 trial reported a 68% reduction in treated bleeds with emicizumab prophylaxis compared with the pre-emicizumab treatment period when

patients received FVIII prophylaxis (annualised bleed rate 1.5 vs 4.8; rate ratio 0.32; 95% CI: 0.20 to 0.51) (Mahlangu et al. N Engl J Med. 2018;379:811-22).

11.17. The Committee noted that in the HAVEN 4 study, 23/41 patients (56.1%; 95% CI 39.7 to 71.5) reported no treated bleeds and 37/41 (90%; 76.9% to 97.3%) reported zero to three treated bleeds (Pipe et al. Lancet Haematol. 2019;6:e295-e305).

11.18. The Committee noted that an indirect comparison network meta-analysis and sub-group analyses of the intra-patient comparison of the HAVEN 3 trial reported that the total bleed rate was lower with emicizumab prophylaxis compared with FVIII prophylaxis (rate ratio 0.36; 95% credible interval: 0.13 to 0.95) (Reyes et al. Curr Med Res Opin. 2019;35:2079-87). The Committee was made aware of further indirect comparison network meta-analysis evidence reporting a similar rate of treated bleeds compared to valoctocogene roxaparvovec (rate ratio 0.57; 95% CI: 0.22 to 1.47) (Agboola et al. J Manag Care Spec Pharm. 2021;27:667-73). The Committee noted the inherent limitations and lesser quality of such indirect comparison methods.

11.19. The Committee noted that a minimal clinically important difference (MCID) in quality of life (Haem-A-Qual index) was defined as a difference of at least 10 points, and considered that data suggest that the MCID was not achieved with emicizumab, although the Committee noted that caregivers preferred emicizumab compared with intravenous FVIII (Mahlangu et al. N Engl J Med. 2018;379:811-22; Shima et al. Haemophilia. 2019;25:979-87).

11.20. The Committee also noted weekly prophylaxis with emicizumab was given to patients with predominantly severe haemophilia A, of which about half had FVIII inhibitors, in some centres as reported by a “real world” retrospective chart review and considered that this evidence supported increasing use of emicizumab in patients without inhibitors (Ebbert et al. Haemophilia. 2020;26:41-6).

11.21. The Committee considered that there is very strong evidence that emicizumab prophylaxis is more effective at preventing bleeds than on-demand FVIII (based on the HAVEN trials), and that there is strong evidence that emicizumab is either equivalent to or slightly better at preventing bleeds than FVIII prophylaxis. However, the Committee noted that there is little improvement in quality-of-life scores with emicizumab prophylaxis.

11.22. The Committee considered that patients with severe haemophilia A without inhibitors would benefit most from emicizumab prophylaxis, with children potentially gaining the most benefit from a reduction in bleeding rates and the potential to delay and/or prevent lifetime damage by commencing treatment with emicizumab at a young age.

11.23. The Committee considered that further peer-reviewed and published trial data would be required to understand what proportion of patients develop inhibitors after emicizumab prophylaxis and to inform whether sequential use of emicizumab, e.g. initial use in patients without inhibitors and then re-treatment after development of inhibitors if patients were given rescue treatment with FVIII, or once-per-lifetime funded access to emicizumab prophylaxis is appropriate. Members considered that longer term data of emicizumab prophylaxis would assist with understanding the incidence of anti-drug antibodies over a person’s lifetime and assist with understanding the efficacy of FVIII prophylaxis following emicizumab prophylaxis.

11.24. The Committee noted that the subcutaneous formulation of emicizumab requires fewer hospital visits than FVIII prophylaxis, and considered that emicizumab prophylaxis would be preferred over currently funded treatment options for patients with haemophilia A without inhibitors.

11.25. The Committee considered that emicizumab prophylaxis would be administered four-weekly due to the ease and cost associated with this frequency of use.

11.26. The Committee noted the high cost of emicizumab prophylaxis could significantly impact on the Combined Pharmaceutical Budget, if funded for patients with haemophilia A without

FVIII inhibitors. The Committee considered that the proposed Special Authority criteria could omit the requirement for ≥5 bleeds occurring despite episodic FVIII treatment, which is similar to that used in clinical trial eligibility criteria, if funded treatment could be effectively targeted to patients with severe haemophilia A without inhibitors based on the low level of FVIII (<1%). The Committee considered this could however result in funded emicizumab access for some patients with mild or moderate disease.

11.27. The Committee considered that there may be health system and family/whānau benefits from indirect effects of a reduction in bleeding events with emicizumab prophylaxis reduced hospital admission time, reduced requirement for infusion services, reduced caregiver time. The Committee considered that most FVIII product usage would be replaced by emicizumab prophylaxis, although there would be some ongoing usage of FVIII and potentially other agents (FVII) to manage surgeries and bleeding events (including life-threatening bleeds which can incur significant costs to the health system). Members considered that higher FVIII use may still be expected in younger patients. Members noted that assays to test for endogenous FVIII levels may be required and are not available in many laboratories. Members considered that the requirement for assay to monitor emicizumab concentrations for titration of therapy remains uncertain. Members noted that central line placement in children for FVIII treatment has a significant cost including anaesthesia and hours of theatre time in some cases.

11.28. The Committee considered that, of the 135 patients with severe haemophilia A described by the Haematology Subcommittee in January 2019, the supplier's estimates that approximately one-third (44) are children aged <18 years and about 91 are adults were likely reasonable. The Committee considered that emicizumab prophylaxis would be an appealing treatment option and that uptake would be very high in the New Zealand context. The Committee considered that emicizumab prophylaxis could continue for a patient's lifetime in almost all cases, although some patients may develop anti-drug antibodies. The Committee considered that adherence could be 95% based on the long term data from the HAVEN studies (Callaghan et al. Blood. 2021;137:2231-42), noting that many patients are closely cared for by healthcare providers and experience immediate harmful effects of suboptimal management.

11.29. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for emicizumab prophylaxis if it were to be funded in New Zealand for haemophilia A without inhibitors. 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 severe haemophilia A, including patients previously on FVIII prophylaxis
Intervention	Emicizumab 3mg/kg weekly for four weeks (loading dose) and ongoing maintenance of 6 mg per kg every four weeks Adherence 95% (Callaghan et al. Blood. 2021;137:2231-42)
Comparator(s)	Episodic / prophylactic use of FVIII Majority of patients assumed to receive prophylactic FVIII based on supplier submission suggesting 100% of paediatric patients and 80% of adult patients receive prophylactic treatment, administered via venous access port in a hospital setting (although subsequently may be administered at home for some patients)
Outcome(s)	Reduction in number of bleeds requiring treatment; improved quality of life over episodic FVIII treatment; reduction in requirement for infusion services
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

11.30. The Committee considered that Pharmac should seek advice from the Haematology Subcommittee and the Haemophilia Treater's group regarding, in particular:

- what the treatment paradigm for haemophilia A might be if emicizumab were funded in this setting
- the proposed Special Authority criteria for targeting funding of emicizumab for this population with severe haemophilia A without inhibitors
- any changes to the current Special Authority criteria for emicizumab in the population with inhibitors
- the assumptions around direct and indirect health system costs and savings (including any changes in administration requirements venous line placement)
- the likely uptake of emicizumab prophylaxis in this population without inhibitors
- the likely change in FVIII usage in the absence of emicizumab funding in this population without inhibitors

12. Food thickeners – review of community products

Consideration

12.1. The Committee considered the funding of food thickeners in the community for the management of dysphagia, following receipt of evidence and information that was provided in response to Pharmac's request for information released in January 2021.

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

Recommendation

12.3. The Committee reaffirmed its previous **recommendation** that the community funding of food thickeners be **delisted**.

12.3.1. In reiterating its previous recommendation, the Committee noted that:

- people with dysphagia i.e. swallowing difficulties, have a high unmet health need, however, there was insufficient evidence that food thickeners would be expected to address these unmet needs and provide clinically meaningful benefits for people with dysphagia
- there is some evidence of a risk of harm from use of food thickeners in dysphagia, namely reduced fluid intake, undernutrition, and potential reduction in quality of life
- there are large numbers of patients with dysphagia from a range of causes, making it difficult to define a specific patient population that may benefit from food

thickeners noting this would likely represent a substantial cost to the Combined Pharmaceutical Budget.

12.4. The Committee acknowledged that there are inequities in the access to food thickeners in the community that may persist, be changed by, or be exacerbated if Pharmac were to delist food thickeners. However, the Committee considered it was not reasonable to recommend Pharmac continue to fund a treatment for which there is evidence that it can cause harm and poor evidence to support potential health benefits.

Discussion

12.5. The Committee noted that Pharmac sought advice regarding the evidence for use of food thickeners for dysphagia in the community. The Committee noted that Pharmac did not seek advice at this time regarding:

- consideration to widening the range of funded food thickeners, i.e. Pharmac is not seeking an evaluation of the products available
- use of food thickeners in hospital
- pre-thickened food or fluids
- consideration to making any changes to the funding of food thickeners in hospital (through Section H of the Pharmaceutical Schedule).

12.6. The Committee noted that food thickeners are funded for use in hospital and in the community for patients with dysphagia (swallowing difficulties), with community funding restricted to people with motor neurone disease with a swallowing disorder. The Committee noted that this restricted community funding was inconsistent with clinical practice, as dysphagia can occur in conditions other than motor neurone disease.

12.7. The Committee noted the extensive history of clinical advice from PTAC and PTAC Subcommittees for the use of food thickeners in the community. The Committee noted that the Special Foods Subcommittee of PTAC considered the following issues in 2001, which the Committee considered remained relevant:

- A substantial number of patients (potentially tens of thousands) may seek access to food thickeners, if funded; and
- If funded, there would be increased use in private hospitals and rest homes due to cost-effectiveness of obtaining a product on prescription; and
- There is a risk that food thickeners may be used before other alternatives have been trialled; and
- The cost of food thickener would not be prohibitively high for most individuals.

12.8. The Committee noted that the Special Foods Subcommittee of PTAC had further considered the use of food thickeners in dysphagia in 2013 and considered that there was no evidence to suggest any specific group of patients with dysphagia would receive greater benefits from food thickeners than any other group, and noted that the Subcommittee had made a recommendation to delist food thickeners from Section D of the Pharmaceutical Schedule based on weak and low-quality evidence.

12.9. The Committee noted that the New Zealand Formulary indicates use of thickeners either for infants under one year of age with significant gastro-oesophageal reflux, or for children over one year of age with dysphagia, but that the currently funded indication is only for motor neurone disease with a swallowing disorder.

Dysphagia

12.10. The Committee noted dysphagia is a medical term used to describe the symptom of difficulty swallowing food or liquid. The Committee noted dysphagia can be caused by or associated with a range of different diseases and pathological causes among different age groups, and considered that individuals may require different treatment approaches depending on the underlying cause.

12.11. The Committee noted that dysphagia affects the safety and efficacy of swallowing and may increase the risk of aspiration (where swallowed material enters the airways), aspiration pneumonia (a complication of aspiration into the lungs) and mortality. However, the Committee noted that not all aspiration pneumonia is caused by dysphagia. The Committee noted that other undesirable outcomes for dysphagia include reduced oral intake leading to malnutrition and dehydration, reduced quality of life, and increased risk of hospitalisation.

12.12. The Committee noted that dysphagia is relatively common, affecting about 13% of people in the community, about a quarter of people in hospitals, and about 60% of residents in aged care facilities. The Committee considered that the risk of dysphagia becomes more common across a person's lifetime, although it can affect infants and children as well as adults. The Committee noted that most prevalence studies of dysphagia are in older adults, a group with a range of comorbidities. The Committee considered there was a large population with dysphagia from a variety of causes who may seek access to food thickeners and that it was difficult to define those with the greatest need. The Committee noted that Pharmac estimated 50% of people with dysphagia in the community may seek funded access to food thickeners for dysphagia, which could result in uptake by at least 27,000 people and potentially up to 65,000 people in the community over five years; the Committee considered these estimates were reasonable given the challenges in defining this broad and varied population.

12.13. The Committee noted that diagnosis and assessment of dysphagia may depend on an individual's life stage and type of underlying disease but noted that patients may be assessed in hospital or community settings. The Committee noted that about 10% of patients diagnosed with dysphagia in hospital are prescribed food thickeners on discharge. The Committee noted that patients diagnosed with dysphagia in the community include adults in residential aged care facilities affected by oncologic and neurological causes of dysphagia, and babies with persistent gastro-oesophageal reflux disease (GORD).

12.14. The Committee noted that, depending on disease pathology, patients with dysphagia may be referred for a clinical assessment of swallowing by a Speech Language Therapist (SLT) including a videofluoroscopic swallowing study (VFSS) as noted in New Zealand Speech-language Therapy Clinical Practice Guideline on Videofluoroscopic Swallowing Study (VFSS; Revised March 2020) and/or a bedside swallow assessment. The Committee noted that VFSS is performed in radiology departments and therefore would compete with other radiology priorities for resources. Members considered that, while VFSS is considered a gold standard for diagnosis of aspiration, it was unclear whether this would accurately predict the risk of aspiration pneumonia.

12.15. The Committee noted that there are a limited number of Speech Language Therapist in the country and that timely access to Speech Language Therapists can be difficult.

Food thickeners

12.16. The Committee noted that benefits associated with food thickeners for dysphagia are theoretically plausible given the mechanics of swallowing noting that thickening fluids is intended to reduce the speed of bolus flow during swallowing, which is considered useful to reduce the risk of laryngeal penetration and aspiration. The Committee was made aware of a systematic review of short-duration studies which investigated the prevalence of penetration and aspiration according to liquid thickness, and which reported lower prevalence of aspiration with thicker liquids (Newman et al. Dysphagia. 2016;31:232-49). The Committee considered it theoretically plausible that a reduction in the risk of aspiration could as a consequence reduce the risk of aspiration pneumonia.

12.17. The Committee noted Pharmac's request for information regarding food thickeners in January 2021 and that more than a quarter of respondents were Speech-Language Therapists. The Committee noted that responses indicated there is broad use of food thickeners across many diseases and age groups, as recommended by various professional groups.

12.18. The Committee noted that thicknesses of foods and liquids are standardised in the IDDSI framework (The International Dysphagia Diet Standardisation Initiative 2019). The Committee was made aware of international guidelines regarding considerations for use of food thickener in individual patients which were based on clinical opinion and required swallowing assessment (McCurtin et al. J Eval Clin Pract. 2020;26:1744-60).

12.19. The Committee noted that there was no new primary research or clinical trial evidence for food thickeners in dysphagia, including dysphagia in motor neurone disease, and that newly published systematic reviews included previously reviewed primary evidence. The Committee considered that there was no new evidence to support the perceived benefits from food thickeners, and that these perceived benefits remained informed by evidence of short-term response and clinical evaluation (either VFSS or bedside).

12.20. The Committee noted the following recent evidence for effectiveness of food thickeners in dysphagia from three systematic reviews (none of which included new primary evidence):

12.20.1. A systematic review of texture-modified foods and liquids for patients aged 18 years and over with oropharyngeal dysphagia in acute or chronic care who were known to aspirate as demonstrated by VFSS (Beck et al. Clin Nutr. 2018;37:1980-91). The authors investigated outcomes including pneumonia and death, aspiration, dehydration, nutritional status, patient preferences and quality of life (among others) and included randomised controlled trials, guidelines, systematic reviews including Cochrane reviews and qualitative studies in this review.

12.20.1.1. The Committee noted that no studies were identified for texture-modified foods. The Committee noted that only two studies of texture-modified liquids (nectar or honey thickened liquids) were identified and that these were randomised controlled trials published in 2008 which included patients with Parkinson disease and/or dementia. The Committee noted aspiration was confirmed by VFSS; the comparator was a thin liquid, and the interventions used a ‘chin-down’ posture.

12.20.1.2. The Committee noted that one study reported the three-month cumulative incidence of pneumonia was 0.098 in the chin-down posture group and 0.116 in the thickened liquid group (0.084 nectar-thick and 0.150 honey-thick). The Committee noted that the highest cumulative incidence of pneumonia was with honey-thickened fluids.

12.20.1.3. The Committee noted that the other study reported VFSS-identified aspiration was 68% with thin liquid, 53% with honey consistency ($P<0.0001$) and 63% with nectar consistency ($P<0.001$).

12.20.1.4. The Committee noted that the authors of the systematic review reported trends towards a reduction in exacerbations and a reduction in pneumonia, although each was informed by low quality evidence. The Committee also noted a trend towards increased weight loss and dehydration with modified textures compared with normal diet/usual care, and considered this was evidence of potential harm from thickened fluids.

12.20.1.5. The Committee noted that the systematic review was used to update the Danish 2012 national clinical guideline on use of textured modified foods and thickened liquids in adults with dysphagia. The updated recommendation was that “based on the quality of the evidence, assessment of the risk benefit ratio, and perceived patient preferences a weak recommendation against the use of texture modified liquids” is made.

12.21. A Cochrane systematic review of modifying the consistency of food and fluids for swallowing difficulties in dementia (Flynn et al. Cochrane Database Syst

Rev. 2018;9:CD011077), was based on the same two clinical trials as the Beck et al. systematic review and therefore provided no additional evidence.

12.22. An updated Cochrane systematic review of formula-fed healthy term infants up to six months of age with gastro-oesophageal reflux who received food thickener or control (Kwok et al. Cochrane Database Syst Rev. 2017 Dec 5;12(12):CD003211). The Committee considered that this patient group with dysphagia would commonly be seen in primary care in GP clinics, for episodic management, although gastro-oesophageal reflux may be self-resolving and may not require treatment.

12.22.1. The Committee noted that eight trials recruiting a total of 637 infants met the inclusion criteria for the systematic review. The Committee noted there was moderate quality evidence of a reduction in the number of episodes of regurgitation per day with feed thickeners and that the authors reported a reduction of two episodes of regurgitation per day may be clinically significant to caregivers. The Committee considered this evidence showed a potential for use of food thickeners in infants and reflected clinical practice; however acknowledged that regurgitation was a self-resolving phenomenon in this population.

12.23. The Committee also noted the following evidence:

- O'Keeffe et al. BMC Geriatr. 2018;18:167
- Lippert et al. J Hosp Med. 2019;14:315-7
- Wallis et al. Pediatr Allergy Immunol Pulmonol. 2012;25:132-42
- Duncan et al. Curr Gastroenterol Rep. 2019;21:30
- Leder et al. Dysphagia. 2013;28:58-62
- Das et al. UpToDate. 2020. Accessed 22 April 2021.
- Duncan et al. Curr Gastroenterol Rep. 2019;21:30
- Ramakrishnam et al. Curr Gastroenterol Rep. 2002;4:218-24.
- Duncan et al. J Pediatr Gastroenterol Nutr. 2019;68:218-24.
- Gurberg et al. Int J Pediatr Otorhinolaryngol. 2015;79:1827-30
- Piccione et al. Pediatr Pulmonl. 2012;47:447-52
- Steele et al. Dysphagia. 2015;30:2-2
- Diniz et al. Nutr Clin Pract. 2009;24:414-8
- Robbins et al. Ann Intern Med. 2008;148:509-18
- Ozaki et al. Tohoku J Exp Med. 2010;220:41-6
- Foley et al. Age Ageing. 2008;37:258-64
- Campbell-Taylor, I. J Am Med Dir Assoc. 2008;9:523-31
- Coyle et al. J Am Med Dir Assoc. 2009;10:62-6; discussion 79-83
- Horvath et al. Pediatrics. 2008;122:e1268-77
- Huang et al. Cochrane Database Syst Rev. 2002;(3):CD003211
- Garcia et al. Nutr Hosp. 2015;31 Suppl 5:56-66
- Jesus et al. Amyotroph Lateral Scler. 2012;13:538-43
- Pezzana et al. J Nutr Health Aging. 2015;19:947-54
- Rofes et al. Gut. 2013;62:1280-7
- Wright et al. Geriatrics (Basel). 2020;5:9
- Sukkar et al. Front Nutr. 2018 7;5:68
- Hwang et al. Ann Rehabil Med. 2017;41:9-15
- Trelis et al. Nutr Hosp. 2002;17:168-74
- Vilardell et al. Dysphagia. 2016;31:169-79
- Sezgin et al. Eur Arch Otorhinolaryngol. 2018;275:2997-3005
- Miranda et al. Nutr Clin Pract. 2020;35:649-54
- Tomita et al. Dysphagia. 2017;32:449-53
- Tomita et al. Yakugaku Zasshi. 2016;136:1171-6

12.24. The Committee considered that the evidence for food thickeners does not support wider use in practice, that there is a lack of good quality evidence that thickening liquids reduces pneumonia in dysphagia, and that there is some risk that food thickeners may be associated

with reduced fluid intake, undernutrition and potential reduction in quality of life. The Committee considered that the use of food thickeners in practice was often based on expert clinical opinion, in the absence of good quality evidence that all patients with dysphagia would benefit from food thickeners.

12.25. Members considered that thickened fluids may not be in the best interest of all patients in some cases other forms of supportive palliative care for symptom management may be more appropriate. Members also considered that thickened fluids can increase the risk of pneumonia in patients with vocal cord dysfunction who cannot effectively protect their airway and may aspirate thickened fluids. Members considered that patients with severe dysphagia remained at risk of silently aspirating at times when not consuming food and fluids, regardless of the use of thickened products.

12.26. Overall, the Committee considered that the evidence base for food thickeners in dysphagia included poor quality evidence with differing assessments of this evidence by different professional groups (Campbell-Taylor I. 2008; Coyle et al. 2009; O'Keeffe et al. 2018; Lippert et al. 2019). Members considered that reasonable quality evidence could be expected in this setting, given the high prevalence of dysphagia across age groups and disease types.

General

12.27. The Committee acknowledged the clinical input provided in response to Pharmac's request for information and recognised the feedback regarding the inconsistency in access to food thickeners in the community and equity concerns associated with this. The Committee noted that there were likely further inequities due to regional variation in access to Speech-Language Therapists.

12.28. The Committee considered that there was a large potential clinical group with health need due to dysphagia but that this group was hard to define, and additionally that it was not possible to identify a population with the greatest need who could be targeted by funded treatment. The Committee considered that this presented significant fiscal risk with little to no evidence of clinical benefit and evidence of potential net harm.

12.29. The Committee acknowledged the high health need of people with dysphagia but noted that there is no evidence that food thickeners would address the unmet need of patients with dysphagia and some evidence that food thickeners may worsen health outcomes and lead to harm. The Committee reiterated its previous recommendation and support to delist food thickeners from the community funding schedule.