PTAC Pharmacology and Therapeutics Advisory Committee

Objective advice to PHARMAC

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Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 17 February and 18 February 2022

This meeting was held via Zoom

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

PTAC and Specialist Advisory Committees may:

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

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

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

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

Present:

PTAC members:

Jane Thomas (Chair)
Marius Rademaker (Deputy Chair)
Alan Fraser
Brian Anderson
Bruce King
Elizabeth Dennett
Giles Newton Howes
Jennifer Martin
Lisa Stamp
Matthew Strother
Rhiannon Braund
Simon Wynn Thomas
Stephen Munn

Apologies:

Tim Stokes

Guests:

Dr Robyn Manuel (Te Rarawa, Ngāti Kahu, Ngāti Kurī and Te Aupōuri) (Consumer Advisory Committee (CAC) observer)

- Dr Manuel is currently a secondary school teacher living and working in Rotorua. She has a PhD in Chemistry and has been involved in teaching and providing advice to education institutions about issues facing Māori, including Māori health, for many years. Robyn has been appointed as a Māori representative on the CAC.

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

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

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

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

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

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

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

2.1. The Committee reviewed the records of the PTAC meeting held on 18 November & 19 November 2021

2.2. The Committee accepted the record.

3. Action Points

3.1. The Committee reviewed the action points of the PTAC meeting held on 18 November & 19 November 2021

4. Subcommittee/Specialist Advisory Committee Records

Neurological Subcommittee (October 2021)

4.1. The Committee reviewed the record of the Neurological Subcommittee held on 29 October 2021. The Committee noted the recommended funding criteria for the agents reviewed and the high recommendation for the funding of rufinamide for Lennox-Gastaut Syndrome.

Reproductive and Sexual Health Subcommittee (November 2021)

4.2. The Committee reviewed the record of the Reproductive and Sexual Health Subcommittee held on 1 November 2021. The Committee noted the recommendations made by the Subcommittee.

4.3. Members noted in relation to the ring pessary item that a major risk of pelvic prolapse surgery, not included in the record, is one of the complications arising from surgical mesh implantation.

Immunisation Subcommittee (August 2021)

4.4. The Committee reviewed the record and noted the recommendations of the Immunisation Subcommittee meeting held in August 2021.

4.5. The Committee noted that the COVID-19 pandemic had impacted a number of immunisation programmes, resulting in reduced coverage. Vaccines with notable reductions in coverage include human papillomavirus (HPV); diphtheria, tetanus and pertussis (DTaP); *Haemophilus influenzae* type b (Hib); the measles, mumps, and rubella (MMR) childhood programme; and the MMR catch up programme.

4.6. The Committee noted that the overall incidence of meningococcal disease in 2020 was lower than might otherwise have been expected, due to public health measures in place to manage COVID-19.

4.7. The Committee noted that the Subcommittee had provided clinical advice to the Ministry of Health about pre-pandemic influenza H5N1 vaccine in the National Reserve Supply and ESR monitoring of varicella and zoster epidemiology in New Zealand.

4.8. The Committee noted and agreed with the Subcommittee's recommendation that influenza vaccine for people with serious mental health conditions or addiction be listed with a medium priority. The Committee noted the significant health need of people with serious mental health conditions or addiction. The Committee noted that there was not strong empirical evidence for health benefit in this group, however there was good biological and psychosocial plausibility for benefit.

4.9. The Committee noted that the Subcommittee recommended that PCV13 vaccine be listed in the Pharmaceutical Schedule with a 2+1 dosing schedule for children under 5 years of age, with a high priority within the context of vaccines and immunisations. The Committee considered this further under Matters Arising.

4.10. The Committee noted and agreed with the Subcommittee recommendation that the 23 valent pneumococcal polysaccharide vaccine for people over the age of 65 be declined. The Committee noted that in making this recommendation, the Subcommittee considered:

- the low-quality evidence for the efficacy of PPV23 against non-bacteraemic pneumococcal pneumonia;
- inconclusive evidence of efficacy against PPV23 serotypes and invasive pneumococcal disease (IPD);
- the lack of evidence of benefit for Māori and Pacific populations;
- the lack of data in people over the age of 60 years with risk factors for severe pneumococcal disease;
- that the addition of conjugate pneumococcal vaccine 13-valent (PCV13) is likely needed prior to receiving PPV23 for patients to receive any measurable benefit.

COVID treatments advisory group (October 2021)

4.11. The Committee noted the record of the COVID-19 Treatments Advisory Group held on 21 October 2021. The Committee noted the recommendations made by the Advisory Group.

4.12. Members noted that the access criteria for molnupiravir had been reconsidered by the COVID-19 Treatments Advisory Group at its meeting on 13 December 2021.

4.13. Members noted that as the COVID-19 situation in New Zealand continues to evolve and evidence for the effectiveness of these treatments against COVID-19 continues to emerge, the access criteria for the various treatments may need to be reconsidered.

5. Correspondence & Matters Arising

5.1. Trinomia (Polypill) Secondary prevention of cardiovascular events

Recommendation

5.1.1. The Committee **recommended** that Trinomia (polypill) for the secondary prevention of cardiovascular events retain its previous recommendation and remain **cost-neutral** to funding of each agent separately.

Discussion

5.1.2. The Committee reviewed correspondence received by Pharmac with concerns that equity of access to cardiovascular pharmaceuticals and adherence were not being considered in the appropriate manner and requested that the application for Trinomia be reconsidered within a Māori and Pacific health context.

5.1.3. The Committee noted previous considerations from both PTAC and the Cardiovascular Subcommittee (Cardiovascular Subcommittee February 2016, PTAC August 2016, PTAC November 2016, Cardiovascular Subcommittee September 2017 recommending for funding with a medium priority, PTAC February 2018 recommending decline, Cardiovascular Subcommittee May 2019, PTAC August 2019 recommending funding only if cost neutral to each separate agent).

5.1.4. The Committee noted that prior recommendations were based on considerations that: improved adherence with a polypill may not necessarily result in a decrease in health inequity for Māori and Pacific patients; polypills attract reduced pharmacy dispensing charges upon receiving only one pill rather than three separate pills, which may influence whether the medication is more likely to be collected from the pharmacy, potentially leading to improved self-reported adherence; challenges of use of fixed dose combination polypills compared with individual component pills including difficulty in determining a specific agent responsible for causing an adverse effect; the inability to tailor and titrate treatments to specific patient needs, and the risk of some patients being over-prescribed certain agents due to their presence in a fixed dose combination pill.

5.1.5. The Committee also noted that previous considerations were based on evidence using surrogate outcome measures, which the Committee placed less weight on given the known generic limitations and potential inappropriateness of surrogates when trying to define the extent that incremental treatment effects are clinically meaningful. The Committee noted that previously PTAC compared the aggregate cost of the individual treatments with the cost of these treatments in a single pill (a polypill) and considered that when the cost of the polypill is greater, the health outcomes of spending this additional amount should be clear and supported by evidence. The Committee noted that PTAC also previously considered that polypills may be used widely to treat people who are at low and medium risk of cardiovascular disease, and that the evidence reviewed did not demonstrate that there a clear health benefit in these populations.

5.1.6. The Committee noted that the applicant provided additional information in support of their resubmission relating to equity considerations:

5.1.7. Yusuf et al. N Engl J Med. 2016;74:2032-43

5.1.8. Joseph et al. Lancet. 2021;398:1133-46

5.1.9. Munoz et al. N Engl J Med. 2019;381:1114-23

5.1.10. Roshandel et al. Lancet. 2019;394:672-83

5.1.11. Selak et al. Eur J Prev Cardiol. 2016;23:1537-45

5.1.12. Yusuf et al. N Engl J Med. 2021;384:216-28

5.1.13. The Committee noted that none of the evidence provided included specific reference to the Trinomia polypill. The Committee also noted that the Selak et al. paper is one of the few New Zealand studies that investigates equity in the treatment of cardiovascular disease.

5.1.14. The Committee noted that the studies provided by the supplier were variable in their constituent drugs and effects: some included aspirin while others did not; some included a statin while others did not; primary and secondary prevention were not individually described; all-cause mortality was not included; and the majority did not include any New Zealand data. Overall, the Committee considered that the applicability of the studies to the New Zealand patient population was low.

5.1.15. The Committee noted that the applicant had indicated that while the currently registered strengths of Trinomia in New Zealand, all include atorvastatin 20 mg, Te Arai has available for submission to Medsafe a changed medicine application for Trinomia that incorporates a higher atorvastatin dose of 40 mg. The Committee considered that the 20 mg dose of atorvastatin in Trinomia may be too low for some patients, and therefore potentially sub-therapeutic for those at high risk, including some patients of Māori and Pacific ethnicity. The Committee considered that a 40 mg dose of atorvastatin would be beneficial but that fixed dosing does not allow for dose titration for an individual patient's needs, which may lead to a higher incidence of adverse events. The Committee considered that it would welcome an adherence study for Trinomia in the New Zealand population, which included both the 20 mg and 40 mg doses of atorvastatin.

5.1.16. The Committee considered that best current practice would be to initiate treatment using individual agents and titrate the dose until clinical benefit was evident. The Committee considered that the Trinomia polypill could be beneficial for patients who have a therapeutic benefit from each individual component at the specific polypill dose. The Committee also considered that even if the polypill was found to be appropriate, a patient may end up having to take multiple pills to enable dose titration. The Committee also considered that polypills may have relevance in other countries with a less developed heath system, where individual titration is less frequently used.

5.1.17. Overall, the Committee did not consider that the additional information provided by the supplier was sufficient to warrant a change from the Committee's previous cost-neutral recommendations. The Committee considered however that reduced cost at the pharmacy level may increase adherence.

5.2. Pneumococcal vaccines

Application

5.3.1. The Committee noted the Immunisation Subcommittee record in relation to pneumococcal vaccines from its August 2021 meeting, and correspondence in reply from a supplier of pneumococcal vaccine.

Discussion

5.3.2. The Committee noted that the Immunisation Subcommittee had considered a July 2021 report from ESR detailing recent trends in Invasive Pneumococcal Disease (IPD) at its August 2021 meeting. The Committee noted that the Immunisation Subcommittee recommended that a 13 valent pneumococcal vaccine (PCV13) should be included in the Childhood Immunisation Schedule rather than the 10 valent pneumococcal vaccine (PCV10) currently listed. The Committee also considered correspondence from a supplier of a pneumococcal conjugate vaccine in response to the Immunisation Subcommittee record and recommendation.

5.3.3. The Committee noted that three conjugated pneumococcal vaccines have been listed in the National Immunisation Schedule at different times since 2008: PCV7 (Prevenar) July 2008 to June 2011; PCV10 (Synflorix) July 2011 to June 2014; PCV13 (Prevenar13) July 2014 to June 2017; PCV10 (Synflorix) July 2017 to present. The Committee noted that although two of the pneumococcal serotypes (6A and 19A) covered by PCV13 are not covered by PCV10, there is some cross protection from serotypes 6B and 19F, which are covered by PCV10.

5.3.4. The Committee noted that ESR established a threshold for monitoring changes in serotype distribution in children under two years of age, following the reintroduction of PCV10 in July 2017. The threshold was established at 9.1 cases per 100,000 children under two years of age. The Committee noted that the purpose for establishing the threshold for serotypes of interest was to trigger further analysis if the threshold was exceeded. The Committee noted that ESR reported that the rate of 19A cases reached 13.1/100,000 children in June 2021, breaching the threshold for the first time since monitoring began.

5.3.5. The Committee noted that the Subcommittee considered that Māori and Pacific peoples were over-represented in the 19A cases that occurred in 2020 in children under 5 years of age.

5.3.6. The Committee noted that the Subcommittee had considered the ESR provisional 2021 IPD data to 30 June 2021 which showed that all 11 cases with vaccine preventable serotypes (PCV10) amongst children under 5 years of age were 19A. The Committee noted that the Subcommittee considered that serotype replacement has been a theoretical concern since pneumococcal vaccines were introduced, and did not consider that the population benefits of pneumococcal vaccination have been eroded due to serotype replacement.

5.3.7. The Committee noted that the correspondence from the supplier included the vaccination status of children with IPD since 2017. The correspondence outlined that while the incidence of 19A has increased in children under 2 years of age since 2017, there was also an increase in incidence in children 2 – 4 years of age, who would have received either a full PCV13 immunisation schedule or a mixed PCV13 / PCV10 schedule. It further outlined that of the eight serotype 19A breakthrough cases occurring in 2018 and 2019 in fully vaccinated children under 5 years of age, all had received at least one PCV13 dose and six had received 3 to 4 PCV13 doses. The Committee noted that the vaccination status data was not available to the Subcommittee when it considered this matter.

5.3.8. The Committee noted that the Subcommittee considered a study looking at serotype replacement trends following the introduction of pneumococcal conjugate vaccines in Europe, North America and Australia (Løchen et al. Sci Rep 2020;10:18977). The Committee noted that while IPD incidence due to vaccine preventable serotypes had decreased in countries, there had been partial replacement by non-vaccine preventable serotypes. While vaccine effectiveness against vaccine preventable serotypes was observed in infants, there was a wide variation in overall IPD rates across countries associated with serotype replacement.

5.3.9. The Committee noted that the Subcommittee considered that data published since the Schedule change from PCV13 to PCV10 vaccine in 2017 suggests that the cross protection against 19A is not as strong as initially thought.

5.3.10. The Committee noted published journal correspondence about the Belgian experience with changing pneumococcal vaccines (Desmet et al. Lancet Infectious Diseases 2018;18(8):830-1). The Committee noted that Belgium changed its immunisation schedule from PCV7 to PCV13 in 2011, then from PCV13 to PCV10 in 2015. The correspondence reported a rise in overall pneumococcal isolates and serotype 19A isolates from 2017.

5.3.11. The Committee noted commentary about the Latin American experience (Avila-Aguero et al. Expert Review of Vaccines 2017;16(7):657-60), which advocated increasing and improving Latin American serotype 19A surveillance, as data from Brazil, Colombia and Chile had suggested a potential increase in serotype 19A infections. The commentary had noted that use of PCV13 in the infant immunisation programme in the United States resulted in a decline of serotype 19A cases in all age groups. The overall IPD incidence declined from 100 cases per 100,000 in 1998 to 2 cases per 100,000 in 2015. The Committee noted from the commentary that England and Wales also experienced decreases in serotype 19A IPD in periods where PCV13 was used.

5.3.12. The Committee noted a retrospective population-based cross-sectional study of the experience of Latvia over seven years (Sevrasova et al. Front Pediatr 2021;9:1-7), indicating serotype replacement with an increasing trend of serotype 19A when using PCV10.

5.3.13. The Committee noted a study from Brazil (Mott et al. Epidemiol Infect 2019;147(e19):1-7) describing the emergence of serotype 19A following the use of PCV10 in the public vaccination programme, with serotype 19A IPD being associated with antimicrobial resistance.

5.3.14. The Committee noted an unpublished report on two retrospective cohort studies of the effectiveness of PCV7, PCV10 and PCV13 in New Zealand in birth cohorts from 2006 to 2019 and 2006 to 2016 respectively (Petousis-Harris et al. 2021; unpublished). The Committee noted that although the authors had concluded in one study that PCV10 and PCV13 were equally effective against otitis media and pneumonia, authors had highlighted that in one of the two transition periods measured that children vaccinated with PCV13 were more likely to be hospitalised with otitis media and possibly all-cause pneumonia compared with those vaccinated with three doses of PCV10, although authors had surmised the group vaccinated with PCV13 may have had a higher proportion of children at higher risk of pneumococcal disease due to comorbidities. The Committee noted that the other study concluded that the use of pneumococcal vaccines in New Zealand has reduced the burden of IPD, otitis media and pneumonia in children under 6 years of age.

5.3.15. The Committee considered that the strength and quality of the New Zealand data reviewed was good, and the strength and quality of the international evidence reviewed was reasonable.

5.3.16. The Committee considered that while there is not yet New Zealand data suggesting that PCV10 and PCV13 are not equivalent at preventing IPD, the accumulating evidence of the international emergence of serotype 19A cannot be ignored. The Committee considered that addressing IPD rates would also have an impact on the burden of otitis media and pneumococcal meningitis. The Committee considered that it would be important to continue surveillance of pneumococcal disease in New Zealand.

5.3.17. The Committee considered that the Immunisation Subcommittee (now the Immunisation Advisory Committee) should review the supplier correspondence and supporting data, including the vaccination status of serotype 19A breakthrough cases and updated reporting from ESR. The Committee considered that the Immunisation Advisory Committee should review this topic again with some urgency to provide an updated view, having taken into account the additional information that is now available.

5.3.18. The Committee noted that higher valent pneumococcal conjugate vaccines are becoming available overseas, such as PCV15 and PCV20.

6. Ferric carboxymaltose (Ferinject) for patients in the community with serum ferritin between 20mcg/L and 50mcg/L where CRP is >5, with the need for GP teams to seek specialist approval

Application

6.1. The Committee noted that Pharmac received a funding application in August 2020 from a clinician seeking to widen access to ferric carboxymaltose for patients with iron deficiency anaemia and inflammation of chronic disease.

Recommendation

6.2. The Committee **recommended** that access to ferric carboxymaltose be widened to include patients with iron deficiency anaemia and inflammation of chronic disease with a **high priority**, subject to the following Special Authority criteria (changes in **bold** and ~~strikethrough~~):

> **Special Authority for Subsidy**
> **Initial application – (serum ferritin less than or equal to 20 mcg/L, or 20 to 50 mcg/L in chronic inflammation)** from any ~~medical~~ **relevant** practitioner. Approval valid for 3 months for applications meeting the following criteria:
> Both:
> 1. Patient has been diagnosed with iron-deficiency anaemia**; and**
> **1.1. S**erum ferritin level **is** less than or equal to 20 mcg/L**; or**
> **1.2. Both:**
> 1.2.1. **Serum ferritin is between 20 and 50 mcg/L** and
> **1.2.2. C-Reactive Protein (CRP) is ≥5 mg/L; and**
> 2. Any of the following:
> 2.1. Patient has been compliant with oral iron treatment and treatment has proven ineffective; or
> 2.2. Treatment with oral iron has resulted in dose-limiting intolerance; or
> 2.3. Rapid correction of anaemia is required.
>
> **Renewal – (serum ferritin less than or equal to 20 mcg/L, or 20 to 50 mcg/L in chronic inflammation)** from any ~~medical~~ **relevant** practitioner. Approval valid for 3 months for applications meeting the following criteria:
> Both:
> 1. Patient continues to have iron-deficiency anaemia with a serum ferritin level of less than or equal to 20 mcg/L **or between 20 and 50 mcg/L with CRP of ≥5 mg/L**; and
> 2. A re-trial with oral iron is clinically inappropriate.
>
> **Note: Pre-treatment CRP and ferritin results are relevant where patient is receiving treatment for chronic inflammatory disease (eg prednisone).**

6.3. In making this recommendation, the Committee considered the unmet health need of patients with iron deficiency and chronic inflammation; the challenges of diagnosing iron deficiency in this group; and the inequity of access to ferric carboxymaltose infusions in primary care.

6.4. The Committee considered that Pharmac should seek advice regarding this application from the Haematology Advisory Committee, specifically: a review of the evidence for ferric carboxymaltose in patients with iron deficiency anaemia and inflammation of chronic disease with ferritin of less than 100 mcg/L, and advice regarding Special Authority criteria for targeting treatment to the population with iron deficiency and chronic inflammation.

Discussion

6.5. The Committee noted that ferric carboxymaltose (Ferinject) is an intravenous (IV) iron preparation containing 5% (50 mg per ml) elemental iron that can be administered as a single infusion for the treatment of iron deficiency anaemia. The Committee noted that ferric carboxymaltose is listed in Section H (subject to restriction criteria) and is listed in Section B of the Pharmaceutical Schedule for the treatment of iron deficiency anaemia (prescribed by or on the recommendation of a specialist) and for patients with serum ferritin less than or equal to 20 mcg/L (prescribed by any medical practitioner) subject to Special Authority criteria.

6.6. The Committee noted that the application sought to widen access to ferric carboxymaltose in the community by allowing any practitioner in primary care to prescribe it for patients with iron deficiency anaemia and inflammation of chronic disease (defined as those with serum ferritin between 20 mcg/L and 50 mcg/L with a CRP level of 5 mg/L or greater). The Committee noted the request intended to facilitate easier access to this treatment for eligible patients who, if they were able to access a specialist opinion, could otherwise be prescribed ferric carboxymaltose on specialist recommendation – but clearly cannot in practice receive treatment because they do not have ready access to such specialist services.

6.7. The Committee noted that patients with iron deficiency anaemia who do not meet DHB criteria for funding of ferric carboxymaltose in hospital may have a need to access it in the community, however, patients encounter inequitable barriers due to the requirement for specialist approval and the administration costs of receiving this treatment. The Committee considered that in this population, iron deficiency is undertreated.

6.8. The Committee considered that specialist endorsement may be sought inconsistently around the country and that self-funding (where feasible for a given patient) results when unfunded treatment administration costs are passed on to the patient. The Committee considered that these access inequities are particularly challenging for patients with reduced access to specialist services and those living in rural areas.

6.9. The Committee considered that enabling primary care prescribers to manage ferric carboxymaltose treatment without seeking specialist endorsement would be beneficial.

6.10. The Committee noted that this widening of access would not address the broader access issue of self-funding treatment administration costs in the community, however, considered that prescribing ferric carboxymaltose in primary care for this subset of patients would streamline the application process and alleviate some pressure on primary care and specialists, whilst enabling access for appropriate treatment of patients with iron deficiency and potentially helping to address undertreatment.

6.11. The Committee considered that the population with iron deficiency anaemia and inflammatory disease would primarily be those with inflammatory bowel disease (IBD) or rheumatological diseases who have a C-reactive protein (CRP) level of 5 mg/L or greater. The Committee considered that these groups of patients are iron deficient (their ferritin, an acute phase protein, is increased by the inflammatory condition) and experience an unmet health need due to their iron deficiency. Members considered that iron deficiency in these groups with chronic inflammation is often poorly recognised and not well managed with oral iron. Members further considered animal studies showing the potential for increased mucosal inflammation from oral iron therapy and considered oral iron therapy may increase the risk of IBD relapse or worsening of disease status (based on anecdotal evidence).

6.12. The Committee considered that patients with chronic heart disease (CHD) or chronic kidney disease (CKD) may also have iron deficiency anaemia that would obtain clinical benefit from ferric carboxymatose. These patients would continue to need endorsement by relevant specialists as per current special authority.

6.13. The Committee considered that the target group of patients could reasonably be defined as having a CRP of >5 mg/L and ferritin of up to 50 mcg/L, as proposed by the applicant, given that a patient with chronic inflammatory disease and ferritin of less than 50 mcg/L would be expected to develop anaemia and become symptomatic. The Committee considered that, for the purposes of targeting a group for funding, no confirmed diagnosis of chronic disease would be required, nor would any other laboratory tests be required. The Committee considered that treatments for chronic inflammatory disease (eg prednisone) would impact on CRP results and therefore pre-treatment CRP and ferritin test results would be relevant. The Committee considered that in general, a timeframe of about three to six months from the test to application for funding would be expected in

clinical practice, however, considered that ferric carboxymaltose would remain an appropriate option for an iron deficient patient with chronic inflammatory disease if tested more than six months earlier.

6.14. The Committee noted that the evidence appeared to consist of general reviews and members considered that high-quality clinical trial evidence is unlikely to be forthcoming in this area. The Committee was made aware of evidence from an analysis of a claims database that suggests intravenous iron (N=442) was associated with fewer all-cause hospitalisations and iron deficiency-related hospitalisations compared with oral iron (N=589) in patients with IBD and iron deficiency (380 patients in each group after propensity matching) (Stein et al. Clinicoecon Outcomes Res. 2018;10:93-103). The Committee was made aware of evidence from a prospective, non-interventional, post-marketing study that treatment of 224 patients with iron deficiency and IBD resulted in quality-of-life improvements from a decrease in symptoms and an improvement in clinical scores with alleviation of anaemia symptoms, regardless of CRP level (Stein et al. J Crohns Colitis. 2018;12:826-34).

6.15. The Committee noted that a ferritin threshold of 100 mcg/L is given in clinical guidelines and consensus statements for the treatment of iron deficiency in patients with chronic inflammatory disorders, who have CRP of 5 mg/L or greater (Cappellini et al. Am J Hematol. 2017;92:1068-78; Dignass et al. J Crohns Colitis. 2015; 9:211-22). The Committee noted that the IRON CORE working group (Cappellini et al.) was convened and supported by industry, however, considered that it provided reasonable statements for patients with chronic inflammation. Overall, the Committee considered that ferritin thresholds of 50 mcg/L or 100 mcg/L may be somewhat arbitrary thresholds for treatment of iron deficiency in patients with chronic inflammation and that it was uncertain what evidence, if any, would support their use for determining eligibility to funded treatment. On balance, the Committee considered that ferritin of 50 mcg/L was reasonable for funded access to ferric carboxymaltose in the context of chronic inflammatory disease with iron deficiency.

6.16. The Committee considered that widening access to ferric carboxymaltose in this way could increase eligible patient numbers by approximately 5-10%. The Committee noted that a CRP level of 5 mg/L or greater may occur in other health states with an inflammatory component (eg obesity, current influenza infection). However, the Committee considered that in practice ferric carboxymaltose would only be prescribed for those who would genuinely benefit, noting that there are barriers to overcome, and therefore it is unlikely to be overused.

6.17. The Committee considered that Pharmac should seek advice regarding this application from the Haematology Advisory Committee, specifically: a review of the evidence for ferric carboxymaltose in patients with iron deficiency anaemia and inflammation of chronic disease with ferritin of less than 100 mcg/L, and advice regarding Special Authority criteria for targeting treatment to the population with iron deficiency and chronic inflammation.

7. Empagliflozin for the treatment of chronic heart failure with reduced ejection fraction, as add-on to optimal standard chronic heart failure treatments, in patients with NYHA class II-IV and LVEF ≤40%

Application

7.1. The Committee reviewed the application from Boehringer Ingelheim New Zealand Limited for the use of empagliflozin (Jardiance) for the treatment of chronic heart failure (CHF) with reduced ejection fraction (HFrEF), as an add-on to optimal standard CHF treatments, in patients with NYHA class II-IV and left ventricular ejection fraction (LVEF) ≤40%.

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 empagliflozin for the treatment of HFrEF, as an add-on to optimal standard CHF treatments, in patients with NYHA class II-IV and LVEF ≤40% be **declined**. In making this recommendation, the Committee considered the limited evidence of the benefit of empagliflozin for HFrEF patients above currently funded treatments, with difficulty in translating this evidence into the New Zealand setting.

7.4. The Committee requested advice from the Cardiovascular Advisory Committee regarding interpretation of the evidence, specifically regarding the health benefit of empagliflozin in the New Zealand population, and whether there is a subgroup of individuals who would benefit from empagliflozin, such as Māori or Pacific peoples, including patient number estimates for these populations.

Discussion

Māori impact

7.5. The Committee noted that HFrEF disproportionately affects Māori, with the heart failure mortality rate among Māori being more than twice as high as that of non-Māori (RR 2.36; CI 1.76 to 3.17), and heart failure hospitalisation rates for Māori being about 4 times that of non-Māori (RR 4.01; CI 3.83 to 4.21) (New Zealand Ministry of Health: Health Status Indicators. 2018). The Committee considered the cause for the disproportionate prevalence and impact of heart failure in Māori is multifaceted, and that key contributing factors may include risk factors (eg smoking, nutrition, alcohol, exercise), the presence of comorbidities (eg hypertension, diabetes mellitus, renal insufficiency, chronic obstructive pulmonary disease, psychiatric disorders), socioeconomic factors, and barriers in access to healthcare (New Zealand Ministry of Health: Ngā tauwehe tūpono me te marumaru: Risk and protective factors. 2021). The Committee also noted that heart failure falls into the Pharmac Māori health area of focus: *Manawa Ora* Heart Health – high blood pressure and stroke.

7.6. The Committee considered, however, that it is unclear what incremental benefit empagliflozin would have in Māori patients with HFrEF given the lack of evidence available for this population group. The Committee also considered that some Māori may already be receiving empagliflozin for the management of diabetes. It was also noted that Māori are impacted by heart failure at a younger age than for non- Māori, on average 10-15 years earlier than for non-Māori.

Discussion

7.7. The Committee noted that HFrEF includes patients with LVEF ≤40% and occurs due to loss of systolic function, which leads to reduced end-organ perfusion, activation of neurohormonal and inflammatory systems, cardiac remodeling (left ventricular dilatation, myocyte hypertrophy, and myocardial fibrosis), and worsening cardiac function which may result in hospitalisation, increased morbidity, and eventual death (Ponikowski et al. 2016. Eur Heart J. 2016;27:2129-2200; Bozkurt et al. J Card Fail. 2021;21; Atherton et al. Heart Lung Circulation. 2018;24:1123-1208).

7.8. The Committee noted that the estimated prevalence of diagnosed HF was 1.6 per 100 persons in the 2020/21 New Zealand Health Survey (NZHS) conducted by The Ministry of Health (NZHS. Ministry of Health. 2021). The Committee noted that the supplier estimated a total of 35,663 patients with NYHA class II-IV HFrEF in New Zealand, which was calculated based on the 2020 New Zealand Health Survey (NZHS) prevalence rate for heart failure (2.2%), and the proportions of patients with HFrEF (51%) and NYHA class II-IV heart failure (80%) (NZHS. Ministry of Health. 2021; Lam et al. Eur Heart J. 2018;20:1770-1180).

7.9. The Committee noted that the supplier estimated mortality and hospitalisation rates of HFrEF in NZ using Lam *et al.* (2018) (Lam et al. Eur Heart J. 2018;20:1770-1180). The Committee noted that using Kaplan-Meier survival curves, the supplier estimated a total of 4,513 deaths in 2021 due to HFrEF based on the prevalence estimate of 35,663, and the mortality rate estimate of 12.7% after one year of follow up. The Committee noted that based on a systematic review and meta-analysis of the survival of patients with CHF in the community setting, the pooled survival rates at 5 years was 56.7% (95% confidence interval [CI] 54.0 to 59.4) and the 10-year survival rate was 34.9% (95% CI 24.0 to 46.8) (Jones et al. Eur J Heart Fail. 2019;11:1306-1325).

7.10. The Committee noted that patients with HFrEF experience symptoms including breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, reduced exercise tolerance and an increased time to recover after exercise, fatigue and tiredness, and ankle swelling (Zambroski et al. Eur J Cardiovasc Nur. 2005;3:198-206; Zhang et al. Int J Cardiol. 2016:676-84; McHorney et al. Plos One. 2021;3:e0248240). The Committee noted this condition results in a negative impact on quality of life for patients that correlated with worse prognosis and early mortality (Iqbal et al. Eur J Heart Fail, 2010;9:1002-1008; Moradi et al. Heart Fail Rev. 2020;6:993-1006). The Committee considered there is a severe unmet health need for patients with HFrEF, particularly in those diagnosed with NYHA class IV who often require full time carers. The Committee noted that HFrEF also has a significant impact on the friends, family, and whānau of patients living with this condition.

7.11. The Committee noted that the currently available treatment options for patients with HFrEF includes loop diuretics, angiotensin-converting-enzyme inhibitors, angiotensin receptor-neprilysin inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, and beta blockers. The Committee considered that sodium-glucose co-transporter 2 (SGLT2) inhibitors are not included in the New Zealand Heart Foundation Guidelines 2018 for the treatment of HFrEF (Heart, Lung and Circulation. 2018;27:1123-1208).

7.12. The Committee noted that the health disparities observed in Māori patients are also reflected in Pacific peoples, who have a prevalence of heart failure of 3.9% (compared to 2.4% of Māori and European/other patients, and 0.9% of Asian patients) (data provided in supplier's submission). The Committee considered that other patient groups, in particular those with limited access to healthcare may also be adversely impacted by heart failure.

7.13. The Committee noted that cardiovascular disease is a government priority condition, and the treatment of heart failure aligns with the Government's strategic priority to improve health outcomes for New Zealanders with long-term conditions.

7.14. The Committee noted that empagliflozin reversibly inhibits SGLT2 in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion (Jardiance Medsafe Datasheet 2019). The Committee noted that empagliflozin is not approved for treatment of cardiovascular disease in patients who do not have a type 2 diabetes mellitus diagnosis. It was noted that Boehringer Ingelheim has submitted an application (Nov 2020) to Medsafe to expand the indications for empagliflozin to include the treatment of HFrEF (note: the proposed indication has since been approved by Medsafe). The Committee noted that the supplier has recommended a dose of empagliflozin of 10 mg once daily for the treatment of HFrEF. The Committee noted that the proposed treatment algorithm provided by the supplier suggests use of empagliflozin as an add-on treatment to currently funded medicines.

7.15. The Committee noted that the key evidence for empagliflozin in the treatment of HFrEF comes from the following clinical trials:

7.15.1. The Committee noted that the EMPEROR-Reduced trial is a randomised, double-blind, placebo-controlled, parallel group, event driven trial which investigated the efficacy of empagliflozin in 3730 patients with HFrEF (NYHA class II-IV). The Committee noted that

after a median follow up of 16 months, the primary outcome of number of deaths from cardiovascular causes or hospitalisations for heart failure was 361 (19.4%) in the empagliflozin group versus 462 (24.7%) in the placebo group (hazard ratio [HR], 0.75; 95% confidence interval [CI] 0.65 to 0.86; P<0.001). The Committee noted the effect of empagliflozin on the primary outcome was consistent in patients regardless of the presence or absence of diabetes. The Committee noted that the total number of hospitalisations for heart failure was lower in the empagliflozin group than in the placebo group (HR, 0.70; 95% CI, 0.58 to 0.85; P<0.001), and that the change in quality-of-life score was greater in the empagliflozin group (5.8±0.4) versus the placebo group (4.1±0.4) (HR 1.7; 95% CI 0.5 to 0.95). It was also noted that uncomplicated genital tract infection was reported more frequently in the empagliflozin group (Packer et al. N Engl J Med. 2020;15:1413-1424).

7.15.2. The Committee was made aware of the Empire HF trial; an investigator-initiated, multi-centre, double-blinded, placebo-controlled, randomised trial which investigated the efficacy of empagliflozin in 190 patients with HRrEF (NYHA class I-III). The Committee noted that after 12 weeks of treatment, no significant difference in the change of NT-proBNP with empagliflozin versus placebo was observed. The Committee also noted that no significant difference was observed in accelerometer-measured daily activity level or Kansas City Cardiomyopathy Questionnaire Overall Summary Score (Jensen et al. Am Heart J. 2020;228:47-56; Jensen et al. Trials. 2019;20:374).

7.16. The Committee considered that the evidence provided shows that empagliflozin does not provide a clinically important additional health benefit over currently available treatments. The Committee considered that the results of these studies are difficult to translate to the New Zealand population given that study participants in the Empire HF study were 85% male and 98% Caucasian, and those in the EMPEROR-Reduced trial were 76% male and 70% white with no Māori or Pacific peoples included.

7.17. The Committee considered that the trial results show that empagliflozin reduces hospitalisation rates in patients with HFrEF. The Committee noted, however, that a reduction in hospitalisation may reflect changes to clinical practice rather than being a proxy for actual treatment benefit for a patient. The Committee considered inpatient hospital management of HFrEF patients is often regarded as the optimal setting, especially for patients with co-morbidities, noting high carer burden and limited resourcing in primary care. Hospitalisation should ideally also involve a review of medication efficacy. An improvement in diuretic therapy for example could outweigh the potential benefit from empagliflozin. The Committee considered that hospital care can be beneficial in ensuring patients with HFrEF are provided with appropriate therapy and ongoing support in the community.

7.18. The Committee considered that the trial results indicated that the impact of empagliflozin on cardiovascular mortality in HFrEF patients is uncertain. The Committee considered that the health benefit of empagliflozin treatment may also be dependent on the NYHA class, with NYHA II patients likely experiencing greater long-term benefit.

7.19. The Subcommittee noted the publications below that reported key clinical trial evidence for other SGLT2 inhibitors for the treatment of HFrEF to assess whether there is a class effect. The Subcommittee considered that a class effect may be likely with regards to hospitalisation rates, however that the biological plausibility, other than from diuresis, is unclear.

7.19.1. The Committee noted that the DAPA-HF trial was an international, multicentre, parallel group, randomised, double-blind, event-driven trial which investigated the efficacy of dapagliflozin compared to placebo in 4744 patients with HFrEF. The Committee noted that the primary outcome for this study was a composite of worsening heart failure (hospitalisation or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death. The Committee noted that after a median follow up of 18.2 months the primary outcome occurred in 386 patients (16.3%) in the dapagliflozin group versus

502 patients (21.2%) in the placebo group (HR 0.74; 95% CI 0.65 to 0.85; P<0.001). The Committee noted that among patients with HFrEF, the risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin than placebo, regardless of the presence or absence of diabetes (McMurray et al. N Engl J Med. 2019;21;1995-2008).

7.19.2. The Committee noted that the CANDLE trial is a post hoc analysis of the investigator initiated, multicentre, prospective, randomised, open-label, blinded-endpoint trial which investigated the efficacy of canagliflozin versus glimepiride in 250 patients with type 2 diabetes with CHF (NYHA class I-III). The Committee noted that the change in NT-proBNP levels at 24 weeks after treatment was 0.98 (95% CI 0.89 to 1.08) in the canaglifozin group versus 1.07 (95% CI 0.97 to 1.18) in the glimepiride group (Tanaka et al. Cardiovasc Diabetol. 2021;1:175).

7.19.3. The Committee were also made aware of Zannad *et al*. 2020; a meta-analysis investigating the effect of SGLT2 inhibition on fatal and non-fatal heart failure events and renal outcomes in all randomly assigned patients with HFrEF and in relevant subgroups from DAPA-HF and EMPEROR-Reduced trials. Among the 8474 patients combined from both trials, the estimated treatment effect was a 13% reduction in all-cause death (pooled HR 0.87, 95% CI 0.77 to 0.98; P=0.018) and 14% reduction in cardiovascular death (0.86, 0.76 to 0.98; P=0.027) (Zannad et al. Lancet. 2020;396:819-829).

7.20. Members considered that if empagliflozin were funded, the requirement for an echocardiogram (ECHO) within the Special Authority criteria may impose equity and access issues, particularly for Māori and Pacific peoples. However, members also considered that an ECHO is required for diagnosing HFrEF, and that removing this criterion may create a risk of slippage. The Committee noted that data on sacubitril with valsartan Special Authority criteria indicates that access to ECHOs are an issue for only 10% of Special Authority applications. If funded, some members considered ethnicity access criteria for Māori and Pacific peoples may be appropriate, as these population groups are often diagnosed with HFrEF earlier in life compared to other populations and experience worse health outcomes as a result. However, members noted that there was a paucity of evidence in support of empagliflozin treatment improving outcomes in these population groups. The Committee noted that the supplier proposed the following Special Authority criteria for funding on the Community Schedule:

> **EMPAGLIFLOZIN**
> **Initial application – Empagliflozin in chronic heart failure**
> Applications from any relevant practitioner. Approvals valid without further renewal unless notified for applications meeting the following criteria:
> 1. Patient has heart failure; and
> 2. Patient is in NYHA/WHO functional class II or III or IV; and
> 3. Either:
> 3.1. Patient has a documented left ventricular ejection fraction (LVEF) of less than or equal to 40%; or
> 3.2. An ECHO is not reasonably practical, and in the opinion of the treating practitioner the patient would benefit from treatment; and
> 4. Patient is receiving concomitant optimal standard chronic heart failure treatments

7.21. The Committee considered that non-pharmacological measures may be more effective in improving health outcomes than the use of additional treatments for patients with HFrEF. If empagliflozin were funded, the Committee considered that adding an additional medication to a patient's current regime may also adversely impact adherence and quality of life.

7.22. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for empagliflozin if it were to be funded in New Zealand for HFrEF. 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 NYHA class II-IV and LVEF ≤40%.
Intervention	Empagliflozin, 10mg once daily. Taken as an adjunctive therapy in addition to optimal standard chronic heart failure treatments.
Comparator(s) (NZ context)	Optimal standard chronic heart failure treatments which include: • Angiotensin Receptor-Neprilysin Inhibitors • Angiotensin-converting enzyme inhibitors • Angiotensin II receptor blockers • Beta blockers • Mineralocorticoid receptor antagonists • Diuretics
Outcome(s)	Outcomes to be considered include: • Reduced all-cause mortality • Reduced symptoms of heart failure • Reduced hospitalisations for heart failure • Reduced cardiovascular mortality • Improved renal function • Improvements in health-related quality of life • Adverse effects related to treatment

Table definitions:

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

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

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

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

8. Palivizumab for respiratory syncytial virus (RSV) prophylaxis in the context of COVID-19

Application

8.1. The Committee reviewed a clinician application for palivizumab for respiratory syncytial virus (RSV) prophylaxis in children under the age of 12 months who are at high risk of RSV-related hospitalisation.

8.2. The Committee noted that Pharmac sought advice on this application in the context of:

- The atypical RSV seasons arising from the COVID-19 pandemic and restrictions
- The impact of COVID-19 on the healthcare system and intensive care units in particular
- The disproportionate effect of RSV on Māori and Pacific infants
- A recent clinician application for a Pharmaceutical Schedule listing for palivizumab (Synagis) for RSV.
- PTAC's prior review of palivizumab for the prophylactic treatment of RSV in pre-term infants.

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 palivizumab be funded for the next two RSV seasons (2022/2023), with a view to reviewing funding and eligibility criteria following the 2023 RSV season (i.e. at two years after this recommendation), for RSV prophylaxis of children under the age of 12 months who are at high risk of developing RSV disease, with a **high priority**, subject to the following Special Authority criteria:

> **PALIVIZUMAB – RSV PROPHYLAXIS FOR THE 2022/2023 RSV SEASONS, IN THE CONTEXT OF COVID-19**
> **Initial application** only from a paediatrician. Approvals valid for 6 months.
> Both:
> 1. Infant was born in the last 12 months; and
> 2. Any of the following:
>
> 2.1. Patient was born at less than 28 weeks gestation; or
> 2.2. Both:
> 2.2.1. Patient was born at less than 32 weeks gestation; and
> 2.2.2. Either:
> 2.2.2.1. Patient has chronic lung disease; or
> 2.2.2.2. Patient is Māori or any Pacific ethnicity; or
> 2.3. Both:
> 2.3.1. Patient has haemodynamically significant heart disease; and
> 2.3.2. Any of the following:
> 2.3.2.1. Patient has unoperated simple congenital heart disease with significant left to right shunt (see note a); or
> 2.3.2.2. Patient has unoperated or surgically palliated complex congenital heart disease; or
> 2.3.2.3. Patient has severe pulmonary hypertension (see note b); or
> 2.3.2.4. Patient has moderate or severe LV failure (see note c)
>
> **Note**:
> a) Patient requires/will require heart failure medication, and/or patient has significant pulmonary hypertension, and/or patient will require surgical palliation/definitive repair within the next 3 months
> b) Mean pulmonary artery pressure more than 45 mmHg
> c) LV Ejection Fraction less than 40%

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

- RSV significantly and disproportionately impacts premature infants who are Māori, Pacific, or living in areas with low socio-economic status (deprivation index 8-10) in their first year of life

- The seasonal characteristics of RSV are highly uncertain in the next two years in the context of the COVID-19 pandemic and an atypical season with greater impact than normal RSV seasons cannot be ruled out

- The evidence for palivizumab prophylaxis in this population supports a reduction in hospitalisation in the target population who are vulnerable and already require a high level of health system engagement and support

- In the context of the COVID-19 pandemic, reducing hospitalisations in this target population would be associated with benefits to the health system, given the expected burdens on DHB hospitals and ICUs

- The evidence for other potential benefits (eg reductions in mortality or respiratory sequelae) from palivizumab is of poor quality and weak strength therefore other benefits to individuals remain unquantified

- Equitable and effective implementation of palivizumab prophylaxis will require substantial engagement with the relevant clinical teams and community health providers, and resolution of important logistical challenges regarding its distribution.

8.6. The Committee considered that Pharmac should inform the Respiratory Advisory Committee and the Immunisation Advisory Committee of the Committee's recommendation to fund palivizumab prophylaxis for the target population for the next two RSV seasons and suggested staff seek advice from these Advisory Committees about how palivizumab access could be effectively and equitably implemented.

8.7. The Committee considered that Pharmac could seek advice from relevant clinical teams [eg neonatal intensive care units (NICU), cardiology and respiratory teams, infectious diseases] and community health providers (eg Māori health providers, GPs and rural health providers) to establish an appropriate distribution and implementation approach for the provision of palivizumab prophylaxis for the next two RSV seasons.

Discussion

Māori impact

8.8. The Committee noted that respiratory disease inequitably impacts Māori and is one of Pharmac's Hauora Arotahi (Māori health areas of focus). The Committee noted that RSV-related illness and hospitalisation significantly and disproportionately impacts premature Māori infants in their first year of life, who experience a higher rate of RSV-related hospitalisation compared with European and other (non-Pacific) ethnicities. The Committee noted that Māori infants have a greater relative risk of pre-term birth compared with European infants, and that Māori infants with certain severe congenital heart defects have lower rates of surgical intervention and survival compared with European infants. The Committee considered it important, especially given the disproportionate risk of prematurity and impact of congenital heart defects for Māori, to avoid disrupting care of premature infants already in hospital (especially those with cardiac disease), to better manage the extra care required for at-risk groups of infants, and to prevent and control intra-hospital infection. The Committee noted that the key outcome of benefit from palivizumab was a reduction in hospitalisation and considered that Special Authority criteria for palivizumab should specifically target Māori infants. However, the Committee noted that palivizumab would not address the disproportionate and inequitable impact of RSV on Māori infants. The Committee considered that equitable implementation of palivizumab for RSV prophylaxis would require proactive engagement with relevant parties including Māori healthcare providers and rural healthcare providers, noting that a range of challenges and barriers exist.

Background

8.9. The Committee noted that an application for palivizumab for prevention of serious lower respiratory tract infections (LRTIs) caused by RSV in high-risk infants was reviewed by PTAC and recommended for decline by PTAC at its February 2000, November 2000 meetings. It was formally declined in 2005 by the Pharmac Board.

8.10. The Committee noted that in February 2009, PTAC reviewed a clinician request to allow for a pre-approved Hospital Exceptional Circumstances (HEC) system to allow patients at risk of RSV [infants under 2 years of age with severe chronic lung disease (CLD), with supplemental home oxygen requirements, or in the hospital preparing for discharge with the strong expectation of home oxygen] to access palivizumab. At that time, PTAC recommended it be declined due to the lack of strength and quality of the evidence and poor cost-effectiveness.

8.11. The Committee noted that in July 2021, in response to the urgent need arising from a major increase in circulating RSV following the COVID-19 lockdown, Pharmac authorised DHBs to purchase palivizumab outside of the Pharmaceutical Schedule for high-risk patients that met certain criteria during the 2021 RSV outbreak. The target population was

restricted to manage supply issues at the time whilst enabling access for high-risk patients. In September 2021, Pharmac authorised widening of access for the 2021 RSV season to the intended, limited high-risk patient population.

8.12. The Committee noted that Pharmac received a funding application for palivizumab for RSV prophylaxis from a clinician in July 2021 and was seeking the Committee's advice on this application in the context of the COVID-19 pandemic.

Discussion

8.13. The Committee noted that RSV is the dominant respiratory virus accounting in New Zealand for about half of all cases of bronchiolitis, an acute respiratory infection, in infants and young children (Prasad et al. Epidemiol Infect. 2019; 147: e246; Alansari et al. Pediatrics. 2019;143:e20182308). The Committee noted that RSV infects a large proportion of children who are less than one year of age, including many under three months or six months of age, and considered this was important, given the exponential lung development that occurs in the first year of life. The Committee noted that RSV cases present with symptoms of respiratory distress (predominantly wheeze), that the virus affects more boys than girls, and that RSV-related illness is treated with supportive care.

8.14. The Committee noted that RSV disproportionately impacts indigenous populations worldwide. Respiratory disease is known to have an inequitable impact on Māori and is one of Pharmac's Hauora Arotahi (Māori health areas of focus). The Committee noted that RSV-related illness and hospitalisation disproportionately impacts premature Māori infants in their first year of life. The Committee noted that RSV-related hospitalisation was higher in Māori children [rate ratio (RR) 4.0, 95% CI: 3.4 to 4.7] compared with European or other ethnicities (Prasad et al. Pediatr Infect Dis J. 2020;39:e176-e182). The Committee was made aware of evidence of infants admitted to a New Zealand paediatric intensive care unit with bronchiolitis from 1991 to 1994; members considered this suggested that Māori infants with RSV are disproportionally represented in these admissions. Members noted however that there was no difference based on ethnicity for patients who required respiratory support (Gavin et al. N Z Med J. 1996;109:137-9). The Committee noted that Māori women had a greater relative risk of having extremely or very preterm infants than European women, and that the relative risk of neonatal death or post-neonatal death was higher in Māori women than European women (Edmonds et al. Int J Gynaecol Obstet. 2021;155:239-46). The Committee noted that, although Māori infants may not have higher rates of CHD than non-Māori, there is evidence that Māori infants with certain severe congenital heart defects have lower rates of surgical intervention and lower survival rates compared with European infants (Cloete et al. Arch Dis Child. 2019;104:857-62).

8.15. The Committee noted that RSV also disproportionately impacts premature Pacific infants in their first year of life. The rate of RSV-related hospitalisation was also higher in Pacific children (RR 2.9, 95% CI: 2.5 to 3.4) compared with European or other ethnicities (Prasad et al. 2020). Members noted that, like Māori infants, Pacific infants and Indian infants are overrepresented in the incidence of pre-term births (Edmonds et al. 2021). The Committee noted that no New Zealand-specific data were available for the rates of RSV-related hospitalisation in Indian infants. The Committee noted that living in an area of low socio-economic status (SES) (deprivation index 8 to 10) independently increased the risk of an RSV-associated hospitalisation in children (RR 1.3, 95% CI 1.0 to 1.6) (Prasad et al. 2020). Given the evidenced increase in risk of RSV-associated hospitalisation for infants in areas of high deprivation, the Committee considered it could be appropriate to target these infants for funded treatment.

8.16. The Committee noted that premature infants, infants with lung disease, and infants with CHD are the patient groups most at risk of RSV-related hospitalisation. Members noted there is ongoing debate regarding whether infants who are immunocompromised, have

neuromuscular disorders, have trisomy 21, or require long-term ventilation have the same elevated risk of RSV-related hospitalisation.

8.17. The Committee considered that hospitalisation itself adversely affects normal family/whānau functioning and that hospitalisation for RSV further impacts family/whānau where children are usually transferred to large treatment centres (eg Auckland's Starship Hospital) for care. The Committee noted the family/whānau impact of hospitalisation for RSV was reported in a study of caregivers of pre-term US infants hospitalised with RSV, who experienced stress, poor health and productivity loss at discharge, and were emotionally impacted, had disruption of family routine, financial concerns and medical concerns continue after discharge (Pokrzywinski et al. Clin Pediatr (Phila). 2019;58:837-50).

8.18. The Committee noted that RSV typically circulates annually in the winter season from May to October in New Zealand and that in Auckland, laboratory-confirmed RSV cases peak at about 50 cases per week, contributing substantially to the number of hospitalisations for acute bronchiolitis (Prasad et al. 2019). The Committee noted that the authors of this Auckland-based study reported that half of RSV-related hospitalisations were in children under six months and that that hospitalisation due to RSV was 30 times as likely in children less than three months of age compared with children aged two to five years. The Committee noted that from 2012 to 2015, 5,309 overnight hospitalisations (median 2 days duration) were reported for acute respiratory infection among children aged under five years, with 433 (8.2%) admitted to intensive care units (ICU). The Committee considered that this reflected the substantial health resource needed to care for young children hospitalised with RSV and the high rate of paediatric ICU (PICU) admissions that result. However, the Committee considered that further health resources are required for infection prevention and control measures, as RSV can spread rapidly within hospitals, and noted that unwell infants including those at high risk of RSV-related hospitalisation already require substantial care and engagement with neonatal facilities in hospital.

8.19. The Committee considered that mortality from RSV is low in New Zealand, noting a recent study reported the rate of death among RSV-positive children was 0.18% (n=3), compared with the rate of all-cause mortality among all patients admitted overnight for acute respiratory infection (0.4%, n=19) (Prasad et al. 2019). However, the Committee noted that some infants hospitalised with RSV are assumed to experience an increased risk of death, ranging from 3.72% to 4% for CHD and CLD patients, respectively, and 0.43% for premature babies (less than 32 weeks gestational age) without CHD and CLD (Wang et al, Health Technol Assess. 2008). The Committee noted the evidence for a reduction in mortality following hospitalisation in infants hospitalised for RSV who received palivizumab compared with those who received placebo, no intervention, or standard care (two-year all-cause mortality relative risk [RR] 0.69, 95% CI 0.42 to 1.15; Garegnani et al. Cochrane Database Syst Rev. 2021;11(11):CD013757). The Committee was made aware of weak evidence for hospital mortality of children with congenital heart disease up to 12 months of age (0.56% in 2012 to 2014 vs 1.93% in 2014 to 2016, $P = 0.051$; Walpert et al. Congenit Heart Dis. 2018;13:428-31). Members considered that hospitalisation in PICU may be associated with increased all-cause mortality and that bronchiolitis could contribute to overall mortality. On balance, the Committee considered the difference in the mortality risk for hospitalised infants with RSV compared with infants in the community with RSV was very low.

8.20. The Committee noted that a very small minority of infants and children can have virus-associated encephalopathy and cardiomyopathy and some may have mild respiratory damage after RSV infection, lasting three to four months. Members considered that two or three children with RSV per year (especially those with pre-existing lung pathology) develop long-term lung pathology from ventilation treatment. The Committee considered that ongoing effects such as wheeze, subsequent bronchiolitis, and an increased risk of RSV infection generally last up to one year and would not require significant intervention or treatment. The Committee considered that the association between RSV infection and

asthma post-RSV was uncertain and that a possible link was likely to be complicated by other factors.

8.21. The Committee noted that the public health measures, border closures and restrictions used in response to the COVID-19 pandemic resulted in a lack of circulating RSV and no noteworthy 2020 RSV season. The Committee noted that alleviation of these measures and the lack of previous exposure to RSV for infants led to a larger and longer atypical 2021 season of RSV circulation which peaked at about 1,000 laboratory-confirmed RSV cases per week in Auckland (compared to previous peak of about 50 cases per week). The Committee noted that 2021 season put enormous pressure on secondary care, impacting on hospitals and ICU beds, caused staff and family sickness, led to elective surgery cancellations and intra-hospital spread. The Committee noted that primary care including GP and nurse teams managed the vast majority of RSV cases in 2021 which impacted the ability of primary care to provide usual care (eg resulting in deferral of routine smears and diabetes reviews).

8.22. The Committee considered that the COVID-19 response applies similar pressures to both primary and secondary care services, with limited capacity for ICU care of infants with RSV requiring hospitalisation. The Committee considered that an increase in morbidity and mortality in some populations would be expected if an RSV season overlapped with COVID-19 circulation (eg leading to dual RSV and COVID-19 infections in critically ill inpatients) and that premature infants may be at greater risk if hospitals are at capacity treating COVID-19 cases. The Committee considered that future RSV seasonality is uncertain but, given the atypical RSV seasons overseas, that it was possible New Zealand would also experience an atypical future season or out-of-season surge with greater impact than typical RSV seasons. The Committee considered that significant health system resource would be needed to manage an atypical RSV season in the context of the COVID-19 pandemic response and that reducing hospitalisation was a key area of need for the health system.

8.23. The Committee noted that palivizumab is a humanised IgG1 monoclonal antibody that is Medsafe- approved for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease. The Committee noted that palivizumab is administered in a dose of 15 mg/kg intramuscularly and should be given monthly during anticipated periods of RSV risk in the community. The Committee noted that palivizumab has been recommended for RSV prophylaxis in some international jurisdictions (eg UK, Canada, Australia), in paediatric clinical guidelines (eg UK and USA) and considered that the jurisdictions reporting better cost-effectiveness with palivizumab had targeted access to populations most at risk of RSV-related hospitalisation. The Committee noted that palivizumab had recently been recommended for at-risk preterm infants in the context of COVID-19 by NHS England and the American Academy of Pediatrics. The Committee noted that other agents such as motavizumab and nirsevimab are being investigated for prevention of RSV-related illness and hospitalisation.

8.24. The Committee noted that little new evidence had been published since its review of palivizumab in 2009. The Committee noted a recent Cochrane review including five randomised controlled trials that assessed the effects of palivizumab (15 mg/kg once a month for a maximum five doses) compared with placebo, no intervention or standard care for preventing severe RSV infection in children (Garegnani et al. Cochrane Database Syst Rev. 2021;11(11):CD013757). The Committee noted that the review included 3,343 children aged zero to 24 months of age regardless of RSV infection history and that one study also included hospitalised infants, and that most studies were conducted in children with a high risk of RSV infection (comorbidities eg bronchopulmonary dysplasia and CHD).

8.24.1. The Committee noted that hospitalisation due to RSV infection at two years' follow-up was 43 per 1,000 with palivizumab vs 98 per 1,000 with placebo (95% CI: 29 to 62); risk ratio (RR) 0.44, 95% CI 0.30 to 0.64; high certainty evidence). The Committee considered that

this provided evidence of a sizeable reduction in hospitalisation in patient groups that align with the target population for New Zealand.

8.24.2. The Committee noted that all-cause mortality at two years' follow-up was 16 per 1,000 with palivizumab vs 23 per 1,000 with placebo (95% CI 10 to 27). The RR (0.69, 95% CI 0.42 to 1.15) was not statistically significant.

8.24.3. The Committee noted that secondary outcomes included hospitalisation due to respiratory-related illness, length of hospital stay, number of wheezing days at one-year follow-up, RSV infection at two years follow-up and outcomes relating to ventilation, ICU stays and supplemental oxygen, with most reporting or suggesting some reduction. The Committee considered that the assessment of RSV infection in the community at two years would be hard to quantify; that the number of wheeze days at one year's follow-up would be of less relevance, and that there was no evidence of an indirect reduction in mortality for RSV patients in the community from a reduction in hospitalisations.

8.25. Members noted that a randomised, double-blind, placebo-controlled trial of 1,287 children with CHD (previously reviewed by PTAC in 2009) reported that palivizumab recipients had a 45% relative reduction in RSV hospitalizations (*P*=0.003) (Feltes et al. J Pediatr 2003;143:532-40). Members noted that respiratory dysfunction was reported for several months after RSV infection and that patients who had surgery during or immediately after RSV infection had a slight increase in morbidity and a greater need for supplemental oxygen and medication. Members considered RSV infection was known to contribute to surgical delays and complicated diagnoses in children with CHD, however, considered that the impact of palivizumab on cardiac mortality and morbidity was poorly quantified.

8.26. The Committee also noted the following updated evidence which was available since its last review of palivizumab in 2009.

- Mitchell et al. Pediatr Pulmonol 2006;41:1167-74
- Ambrose et al. Hum Vaccin Immunother. 2014;10:2785-8
- Chi et al. PLoS One. 2014;9:e100981
- Kusuda et al. Pediatr Int. 2011;53:368-73

8.27. The Committee considered that the new evidence supported earlier findings and that palivizumab still appeared to have low cost-effectiveness. The Committee considered that the evidence for palivizumab prophylaxis in this population supports a reduction in hospitalisation in the target population who are vulnerable and already require a high level of health system engagement and support. The Committee considered that the evidence for most other outcomes from palivizumab prophylaxis was poor, especially for specific population groups (eg infants with immunodeficiency, neuromuscular disorders, or trisomy 21) for whom palivizumab is funded in some jurisdictions but expert opinion about its benefits in these groups is varied. Overall, the Committee considered that the evidence for other potential benefits from palivizumab was of poor quality and weak strength, therefore other benefits to individuals were uncertain and it would not be appropriate to consider long term sequelae associated with palivizumab beyond immediate reduction in hospitalisation.

8.28. The Committee considered that although future RSV seasonality was uncertain, in the near future during the COVID-19 pandemic response, a reduction in RSV-related hospitalisations in the target population would be associated with benefits to the New Zealand health system and may help to minimise the risk of hospitalisation during a dual epidemic scenario. However, the Committee considered that longer-term future benefits from palivizumab were uncertain and the longer-term needs of infants at risk of RSV-related hospitalisation and the health system were unclear, due to the uncertain length of the COVID-19 pandemic's impact on New Zealand and its health system. Therefore, the

Committee considered its recommendation for palivizumab should be limited to funding for the next two RSV seasons (2022/2023), with a view to reviewing funding and eligibility criteria two years after this recommendation. The Committee considered this may be difficult to implement within the constraints of the Pharmaceutical Schedule and that consideration of stopping funding after two years would be challenging and likely met with significant resistance.

8.29. The Committee considered that palivizumab would not address the disproportionate and inequitable impact of RSV on Māori and Pacific infants. However, the Committee considered targeting Māori and Pacific infants would support equitable health outcomes across infants at high-risk of hospitalisation. The Committee considered it important to avoid disrupting care of premature infants already in hospital (especially those with cardiac disease), to better manage the extra care required for at-risk groups of infants, and to prevent and control intra-hospital infection. The Committee considered it appropriate for the Special Authority criteria for palivizumab to specifically target Māori and Pacific infants, given the evidence of higher RSV-hospitalisation rates for these groups. The Committee considered that palivizumab could also be targeted to at-risk premature infants living in areas of high deprivation. The Committee considered that about 900 patients per year would meet the proposed criteria.

8.30. The Committee noted that Narayan et al (J Med Econ. 2020;23:1640-52) report an average of 3.7 doses of palivizumab used per infant in a cost-effectiveness analysis, however, the Committee considered the likely average number of doses in upcoming years was uncertain given that the future RSV seasonality and impact is unknown. The Committee considered that an initial Special Authority approval duration of six months would facilitate prophylaxis during typical or even slightly longer seasons and be reasonable for fiscal management in uncertain near-future seasons, noting that the 2021 season was unusually short compared to those reported in other countries and given that clinicians would not administer palivizumab unless it was potentially useful and the season was ongoing.

8.31. The Committee considered that vial sharing would be expected to occur only at larger treatment centres where large numbers of infants present for prophylaxis and that approximately five infants could receive prophylaxis from three 100mg vials. The Committee noted that the shelf-life of palivizumab is 36 months from the date of manufacture.

8.32. The Committee considered that access to clinics for administration would be challenging, requiring family transport to hospital or GP clinics monthly and that this may be significant for infants living in rural area. Overall, the Committee considered that implementation of palivizumab in primary care would be a considerable undertaking with a number of logistic and access issues. The Committee noted that the cost of administration in GP clinics, if not funded, would be passed onto primary care and in turn passed onto family/whānau and would become another access barrier, driving inequity. The Committee also noted the potential challenges of implementation given the pressures from COVID-19 on the healthcare system.

8.33. The Committee considered that equitable and effective implementation of palivizumab in the community and in hospitals would be challenging, noting that some patients may commence treatment in hospital while others may be identified in the community. The Committee noted that many premature infants are well known to NICUs and cardiology departments, and therefore are able to be identified, and that learnings from the 2021 NICU-directed implementation could help to inform implementation for 2022/2023. However, the Committee considered that successful implementation would require substantial engagement with relevant clinical teams (eg NICU, cardiology and respiratory teams, infectious diseases) and community health providers (eg Māori health providers, GPs and rural health providers) with resolution of important logistical challenges regarding its distribution, administration and patient identification. The Committee noted that training, support and funding of injection administration would be needed in primary care.

Members considered that development of a national registry could help with identification and treatment initiation and considered that Pharmac could engage with the Ministry of Health on this. Overall, the Committee considered an equitable, New Zealand-specific process implementation approach was needed and that engagement with primary care, Māori health providers and relevant hospital clinical teams would help inform this. Members considered that it would be important for Pharmac to monitor and review the implementation of palivizumab in 2021 and over the next two years.

8.34. The Committee considered that Pharmac should inform the Respiratory Advisory Committee and the Immunisation Advisory Committee of the Committee's recommendation to fund palivizumab prophylaxis for the target population for a period of two seasons (with a view to review two seasons) and could seek further advice from these Advisory Committees about how palivizumab could be effectively and equitably implemented. The Committee considered that Pharmac should seek advice from relevant clinical teams (eg NICU, cardiology and respiratory teams) and community health providers (eg Māori health providers, GPs and rural health providers) to establish an appropriate distribution and implementation approach for palivizumab.

8.35. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for palivizumab if it were to be funded in New Zealand for RSV prophylaxis. 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	Infants born in the last 12 months and, • Born at less than 28 weeks gestation or, • Born 29 to 32 weeks gestation and has chronic lung disease or, • Born 29 to 32 weeks gestation and is Māori or Pacific • Infant has haemodynamically significant heart disease.
Intervention	Palivizumab 15mg/kg given monthly via IM injection
Comparator(s)	Best standard of care
Outcome(s)	Reduced hospitalisation
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

9. Paracetamol 1000mg/ibuprofen (as sodium dihydrate) 300mg in 100mL solution for infusion for acute pain

Application

9.1. The Committee reviewed the application from University of Auckland for the use of paracetamol 1000 mg with ibuprofen (as sodium dihydrate) 300 mg in 100 mL solution for infusion (Maxigesic IV) for the treatment of acute pain. The Committee noted that additional information was provided from AFT Pharmaceuticals to aid in the assessment of this funding application.

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

Recommendation

9.3. The Committee **recommended** that the funding application for Maxigesic IV be **declined**. In making this recommendation, the Committee considered:

- The evidence presented displayed that Maxigesic IV provided superior analgesia compared to monotherapy IV paracetamol or IV ibuprofen treatment, however that there is insufficient evidence to demonstrate that this is a synergistic as opposed to an additive effect

- The lack of evidence to show that Maxigesic IV would provide a significant health benefit over currently funded treatments or reduce the potential for opioid misuse in the acute pain setting

- The potentially subtherapeutic dose of 300 mg ibuprofen in the Maxigesic IV product and the subsequent risk of treatment failure

9.4. The Committee requested advice from the Analgesics Advisory Committee regarding interpretation of evidence, specifically regarding the health benefit of Maxigesic IV compared to currently funded treatments.

Discussion

Māori impact

9.5. The Committee noted that no evidence was identified linking the incidence of poorly managed acute pain and Māori health outcomes.

Discussion

9.6. The Committee noted that Pharmac received an application for oral paracetamol with ibuprofen in 2010, which PTAC recommended for decline due to lack of evidence of efficacy, safety, or improved compliance when compared with the individual pharmaceutical components taken together.

9.7. The Committee noted that acute pain is experienced as a symptom of many injuries, diseases, and procedures. The Committee noted that the primary aim of acute pain management is to provide treatment that reduces pain with minimal adverse effects, while allowing function to be maintained (after treating the underlying cause of the pain, where possible), and that the secondary aim is to prevent acute pain from progressing to chronic pain (BPAC: The principles of managing acute pain in primary care. 2018). The Committee noted that acute pain is a broad indication with various underlying causes and is not routinely reported by the Ministry of Health, thereby making it difficult to ascertain the incidence of acute pain in the New Zealand population.

9.8. The Committee considered that there is a significant health need for those experiencing acute pain. The Committee noted that when not well managed, acute pain can develop into persistent or chronic pain, which may result in a range of comorbidities including depression, anxiety, poor quality and quantity of sleep, impaired movement, impaired concentration, social restrictions, and relationship difficulties (Swain et al. NZMJ. 2018). The Committee noted that suboptimal perioperative analgesia may result in delayed time to recovery, acute postsurgical complications, and persistent postsurgical pain (Chou et al. J Pain. 2016;2:131-157; Gan et al. Curr Med Res Opin. 2014;1:149-160).

9.9. The Committee noted that there are many funded treatments for acute pain, including non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and other analgesics. The Committee noted that IV paracetamol is available and funded for use in acute pain, and that although IV ibuprofen is listed as “any brand” on the Hospital Medicines List (HML), there is no Medsafe approved IV ibuprofen product available in New Zealand. The

Committee noted that other funded IV NSAIDs include diclofenac sodium and parecoxib. The Committee noted that while IV opioids are efficacious in the treatment of acute pain, they may cause complications due to adverse events including gastrointestinal effects, dizziness, over-sedation, respiratory depression, and opioid induced hyperalgesia.

9.10. The Committee noted that there may be a health need for those caring for family or whānau in acute pain, due to the mental and emotional impact of caregiver burden. The Committee noted, however, that specific evidence quantifying this health need could not be identified.

9.11. The Committee noted that the exact site and mechanism of analgesic action of paracetamol is not clearly defined, however it potentially involves inhibition of the nitric oxide pathway mediated by a variety of neurotransmitter receptors including N-methyl-D-aspartate and substance P. It was noted that ibuprofen possesses analgesic, antipyretic, and anti-inflammatory properties, and is thought to act through peripheral inhibition of cyclooxygenases and subsequent prostaglandin synthesise inhibition. The Committee noted that Maxigesic IV is Medsafe approved for the treatment of acute pain, and that the recommended dose is one vial (paracetamol 1000 mg with ibuprofen 300 mg in 100 mL) via IV infusion over 15 minutes every 6 hours as necessary until switching to oral therapy, with a maximum daily dose of 4000 mg paracetamol. The Committee considered that Maxigesic IV would predominantly be used in patients experiencing acute pain as a result of trauma and in the peri-/post-operative setting.

9.12. The Committee noted that the key evidence for Maxigesic IV for the treatment of acute pain comes from two clinical trials:

9.12.1. The Committee noted that the NCT02689063 trial was a randomised, double-blind, placebo-controlled factorial trial that compared the efficacy of fixed dose combination (FDC) ibuprofen 300 mg and acetaminophen 1000 mg, ibuprofen 300 mg, acetaminophen 1000 mg, and placebo in 276 patients following distal, first metatarsal bunionectomy using pain intensity levels ≥40 mm on a 100 mm visual analogue scale (VAS). The Committee noted that the sum of pain intensity differences (SPID) from baseline over 48 hours ($SPID_{48}$) was significantly higher for the FDC (23.4 mm) than for ibuprofen (9.5 mm), acetaminophen (10.4 mm), and placebo (−1.3 mm; all, $P<0.001$). The superior analgesic effect of the FDC was supported by a range of secondary end points, including reduced opioid usage rates (75% for FDC, 92% for ibuprofen, 93% for acetaminophen, and 96% for placebo; all, $P<0.005$). The safety profile of the FDC was comparable to that of intravenous ibuprofen or acetaminophen alone (Daniels et al. Clin Ther. 2019;10:1982-1995).

9.12.2. The Committee noted that Gupta et al. 2016 was a randomised, single centre trial which compared the efficacy of ibuprofen 800 mg IV monotherapy (Group 1) versus paracetamol 1000 mg IV and ibuprofen 800 mg IV combined therapy (Group 2) in 78 patients undergoing elective knee or hip arthroplasty, with treatment continued until discharge or for up to 5 days. The Committee noted that patients in Group 2 had lower VAS scores ($P<0.002$) by day 3, with significantly reduced opioid requirements and adverse events compared to Group 1. The Committee noted that the results for the time to discharge from the post anaesthetic care unit (PACU), length of hospital stay, and quality of recovery scores were not statistically significant between the two groups (Gupta et al. Pain Physician. 2016;6:349-356).

9.13. The Committee noted the additional studies below describing the use of IV parecoxib combined with IV paracetamol in patients with acute pain as an indirect comparison to patients receiving IV paracetamol/ibuprofen:

- Mulita et al. Med Glas (Zenica). 2021;1:27-32
- Mohamad et al. Anaesth Intensive Care. 2014;1:43-50

- Camu et al. Acta Anaesthesiol Scand. 2017;1:99-110

9.14. The Committee considered that the evidence provided shows that the combination of IV paracetamol and ibuprofen appears to provide superior analgesia compared to IV paracetamol or IV ibuprofen monotherapy, and that there is insufficient evidence to demonstrate a synergistic effect. The Committee considered that the improved analgesia was minimal, and that Maxigesic IV would not provide a significant health benefit over currently funded treatments for acute pain.

9.15. The Committee considered that study results also showed that Maxigesic IV reduced but did not eliminate the need for opioid treatment and considered the potential cost saving from this reduced opioid use to be minimal. The Committee noted that the clinician application stated that reduced use of opiates in the acute pain setting may reduce risk of long-term opioid dependence or misuse. The Committee considered that opioid dependence is related to chronic pain, and that while chronic pain can be influenced by failed therapy in the acute setting, there is no identified evidence to suggest that funding of Maxigesic IV (in addition to currently funded treatments) will impact chronic opiate use.

9.16. The Committee considered that the perception of pain is subjective, dependent on individual differences. Therefore, the comparison of pain scores between individuals in the provided evidence may not provide the best measure of efficacy. Members considered that VAS scores are not designed to be compared between groups, but rather to compare an individual's response to pain over time. Members also considered that the results of the NCT02689063 trial are difficult to translate to the wider New Zealand population of patients experiencing acute pain, given the study population was limited to bunionectomy patients.

9.17. The Committee considered that the dose of 300 mg ibuprofen per Maxigesic IV vial is less than the standard ibuprofen dose of 400 mg, or up to 800 mg in other clinical trials. It was considered that there is no evidence to show that ibuprofen 300 mg is clinically equivalent to 400 mg, and that the ibuprofen dose in Maxigesic IV may be subtherapeutic. The Committee considered that the addition of ibuprofen to a paracetamol regime may also introduce the risk for NSAID-related adverse events, noting that ibuprofen is a non-selective COX inhibitor. Members considered that use of Maxigesic IV may increase the incidence of GI-related adverse events, particularly given that ulceration complications are prevalent in the first week of NSAID use.

9.18. The Committee noted that, based on clinician and supplier advice, parecoxib was used as the comparator for the preliminary economic analysis. The Committee noted that Pharmac staff expressed uncertainty as to whether the most appropriate comparator would be IV parecoxib, IV paracetamol only, or a combination of the two. The Committee considered that parecoxib is a COX-2 specific inhibitor; therefore, it is not directly comparable to ibuprofen (a non-selective COX inhibitor). The Committee considered combination treatment of IV parecoxib and IV paracetamol to be a more appropriate comparator, and that IV diclofenac may be an additional alternative comparator. The Committee also considered the proposed estimate of 2.5 doses of Maxigesic IV per patient to be an underestimate, and that treatment would likely be continued for at least 24 hours.

9.19. The Committee considered the cost savings from reduced opioid use to be an overestimate, as patients treated with Maxigesic IV are likely to require opioid rescue treatment. The Committee considered that any cost savings associated with reduced risk of long-term opioid dependence or misuse should not be included in the economic analysis.

9.20. The Committee considered that the use of a combination product may introduce issues around quality use of medicines, including the inability to titrate doses and the potential for dosing errors. Members considered that the use of Maxigesic IV may reduce the use of infusion administration products and thereby may reduce costs in this area.

9.21. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for Maxigesic IV if it were to be funded in New Zealand for acute pain. 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 experiencing mild to moderate acute pain, where an IV route of administration is deemed clinically necessary. There is no specific population group as acute pain is a symptom of many different conditions and procedures, each of which will have varied characteristics in terms of age, ethnicity, comorbidities, etc.
Intervention	15-minute infusion of paracetamol 1000 mg with ibuprofen 300 mg in a 100 mL vial. Administered every six hours until switching to oral therapy is possible. Patients are likely to remain on treatment for 24 hours, which equates to an average of four vials per patients
Comparator(s) (NZ context)	IV parecoxib 40 mg every 24 hours with IV paracetamol 1000 mg every 6 hours.
Outcome(s)	Greater reduction in pain (as measured by $SPID_{48}$) compared to existing treatments while patients are on treatment, as demonstrated in Daniels et al. Clin Ther. 2019;10:1982-1995.
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

10. Spinal Muscular Atrophy (SMA) Treatments – duration of treatment benefit

Discussion

10.1. The Committee noted that Pharmac was seeking further advice to inform its economic modelling of Spinal Muscular Atrophy (SMA) treatments, in particular the duration of treatment benefit to assume over a lifetime time horizon. The Committee noted that this a complex area with limited evidence to inform economic modelling.

10.2. The Committee also noted that its views on the degree of treatment benefit associated with medicines in this area have been chronicled in previous meeting records, and informed by published evidence and New Zealand clinical expert advice. Consequently, the scope of this discussion was limited to the duration of that treatment benefit.

10.3. To determine the appropriate duration of treatment effect, the Committee considered evidence relating to:

10.3.1. the mechanism of action of medicines in this disease area,

10.3.2. the duration of clinical evidence for the two medicines, and

10.3.3. the strength of clinical evidence, including relationships between surrogate and final endpoints in this disease area and degree of evidenced treatment effect.

10.4. The Committee noted that there are two medicines currently under consideration for the treatment of SMA in New Zealand, nusinersen and risdiplam. The Committee noted that nusinersen and risdiplam have very similar mechanisms of action, and that there is high biological plausibility of an enduring treatment effect based on these mechanisms of action.

10.5. The Committee noted that currently nusinersen has longer-term follow up than risdiplam: the maximum length of results reported from phase three clinical trials are approximately 39 months for nusinersen and 24 months for risdiplam. The Committee considered that this length of evidence is relatively short for a life-long condition, and that the survival data in the clinical trials is extremely immature.

10.6. However, the Committee also noted that the survival and progression free survival outcomes, in SMA type 1 especially, show substantial improvements relative to the natural history of disease. The degree of benefit in this group especially was considered persuasive in terms of the possible impact of the medicines in this area.

10.7. Members noted that SMA is somewhat different to other lifelong conditions in regard to the confidence with which assumptions can be made about long term impacts from available, short-term evidence. Members noted that relationships between surrogate markers and final endpoints (especially survival) have not been formally established in SMA to signal long term benefit, although evidence in this area may become available in the future.

10.8. The Committee considered that given the high biological plausibility of long term treatment effect and the extent of the treatment benefit, especially in SMA type 1, it was appropriate to assume that the duration of benefit from SMA treatments is lifelong, or for the duration of treatment, whichever is shorter. The Committee considered it appropriate to re-evaluate this view if more definitive evidence (eg validated surrogate outcomes, or long-term outcome data) became available.

10.9. The Committee noted the current recommended renewal criteria for ongoing treatment with the SMA treatments. The Committee considered that due to the difference between the renewal criteria and the stopping criteria in trials (ie ventilation), real world discontinuation rates in New Zealand would differ from discontinuation rates observed in the clinical trials, if nusinersen or risdiplam were funded in New Zealand with these renewal criteria.

10.10. The Committee considered that discontinuation of SMA treatment would be unlikely to change over time unless new treatments for SMA became available. The Committee also considered that the majority of people with SMA would be expected to continue treatment of some sort for as long as they lived, based on their physician’s ongoing evaluation of the benefit they were receiving, against the renewal criteria.

10.11. The Committee considered, despite the differences in SMA identified pre-symptomatically and symptomatically, that it would be appropriate to apply the same assumptions regarding a lifelong duration of treatment benefit to all groups. This was because the same arguments around biological plausibility were considered to apply to both subgroups, and the extent of benefit in the two groups has been evaluated and agreed separately.

10.12. The Committee noted that based on previous consideration by PTAC and the Rare Disorders and Neurological Subcommittees, a large proportion of people with SMA would be assumed to have an SMA type 4 phenotype if treated in the pre-symptomatic setting. The Committee considered it important that the morbidity associated with an SMA type 4 phenotype be reflected in economic modelling in the decades after symptom onset with this phenotype, given the recommended assumption of lifelong benefit.

10.13. The Committee also considered that it would be appropriate for the same assumptions to be made for both nusinersen and risdiplam, noting that while data maturity differs between the two agents, the mechanisms of action and consequent biological plausibility of treatment effect are similar.

I certify that this is a true and correct record of the records of the meeting held on held 17 February & 18 February 2022

Signed: _____ Date: _____
Doctor Jane Thomas, Chair