PTAC Pharmacology and Therapeutics Advisory Committee

Objective advice to PHARMAC

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Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 18 May & 19 May 2023

This meeting was held in person and via Zoom

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1. Present:

PTAC members:
Jane Thomas (Chair)
Rhiannon Braund (Deputy Chair)
Alan Fraser
Brian Anderson
Bruce King
Elizabeth Dennett
Giles Newton Howes
Jennifer Martin
John Mottershead
Lisa Stamp
Matthew Dawes
Matthew Strother
Robyn Manuel
Simon Wynn Thomas
Stephen Munn

Apologies:

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

2.1. 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.

2.2. 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.

2.3. 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.

2.4. 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.

3. Summary of recommendations

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

Pharmaceutical and Indication	Recommendation
9.4. palivizumab in the prevention of RSV	**High priority**
10.4. Fixed duration ibrutinib plus venetoclax (I+V) for the treatment of previously untreated Chronic Lymphocytic Leukaemia (CLL) or Small Lymphocytic Leukaemia (SLL) without del(17p)/TP53 for individuals who are not eligible for chemoimmunotherapy.	**High priority**
10.5. fixed duration ibrutinib plus venetoclax (I+V) for the treatment of previously untreated Chronic Lymphocytic Leukaemia (CLL) or Small Lymphocytic Leukaemia (SLL) without del(17p)/TP53 for individuals who are eligible for chemoimmunotherapy.	**Medium priority**
11.4. empagliflozin for the treatment of HFpEF/HFmrEF, as an add-on to optimal standard CHF treatments, in individuals with NYHA class II-IV and LVEF >40%	**Decline**
12.4. silver diamine fluoride (SDF) for the management of dental caries	**High priority**
13.4. octreotide for the treatment of polycystic 0liver disease	**Decline**
14.4. upadacitinib for first line ulcerative colitis	**Medium priority**
14.4. upadacitinib for second line ulcerative colitis	**High priority**
14.4. upadacitinib for the treatment of Crohn's disease	**Deferred**

4. Specialist Advisory Committee Record

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

2022-09-22 Anti-infective Advisory Committee Meeting Record

4.2. The Committee reviewed the record of the Anti-infective Advisory Committee meeting held on 22 September 2022

4.3. The Committee noted the record.

2022-10 Cancer Treatments Advisory Committee Meeting record

4.4. The Committee (PTAC) reviewed the record of the Cancer Treatments Advisory Committee (CTAC) meeting held on 28 October 2022.

4.5. PTAC noted CTAC's discussion regarding Special Authority applications from non-medical prescribers. PTAC acknowledged the multidisciplinary nature of many healthcare teams in Aotearoa New Zealand, with the breadth of roles, perspectives, diversity of patient/whānau engagement, and experience that their different disciplines contribute. The Committee considered prescriber restrictions create barriers to accessing funded medicines and that the need to reduce these barriers was not specific to oncology. PTAC considered that reflecting the multidisciplinary nature of health care teams should be considered across all therapeutic areas.

4.6. The Committee noted the other items discussed at CTAC's meeting held on 28 October 2022.

COVID-19 Treatments Advisory Group combined meeting records for molnupiravir

4.7. The Committee (PTAC) reviewed the combined records of the Ad-hoc COVID-19 Treatments Advisory Group regarding molnupiravir, from meetings held in August 2022, October 2022 and February 2023. PTAC noted the recommendations and considerations of the Advisory Group and had no additional comments regarding these.

4.8. PTAC noted that Pharmac has recently consulted on options to clarify the role of molnupiravir in New Zealand's portfolio of funded COVID-19 treatments, to either stop funding and delist it or to make changes to the eligibility criteria, and that Pharmac expects to finalise a decision in June 2023.

5. Correspondence & Matters Arising

Eribulin for the treatment of advanced or metastatic breast cancer following progression after at least two lines of chemotherapy

Application

5.1. The Committee noted correspondence received from Breast Cancer Aotearoa Alliance (BCAC) and Eisai New Zealand Limited for the use of eribulin for the treatment of advanced or metastatic breast cancer following progression after at least two lines of chemotherapy, in response to PTAC's considerations at its meeting in November 2022.

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

Recommendation

5.3. The Committee reiterated its previous decline recommendation for this application.

Discussion

5.4. The Committee noted that at its' November 2022 meeting, it has considered an application from BCAC for eribulin for the treatment of locally advanced or metastatic breast cancer following progression after at least two lines of chemotherapy. The Committee noted that at this meeting it recommended that this application be declined, noting at the time:

5.4.1. the significant health need of people with advanced or metastatic breast cancer, particularly for Māori and Pacific peoples;

5.4.2. that the evidence was conflicting and of low quality and that the results were not generalisable to the New Zealand population demographic

5.4.3. the less-favourable adverse event profile for eribulin

5.4.4. the minimal evidence of benefit from eribulin for the requested population.

5.4.5. The Committee noted its previous commentary regarding the involvement of the sponsor in many aspects of the clinical trial evidence.

5.4.6. The Committee noted its previous commentary about the generalisability of the evidence to the New Zealand population, primarily Māori or Pacific people with locally advanced or metastatic breast cancer. The Committee acknowledged that a lack of Māori or Pacific ethnicity-specific efficacy data is not uncommon for globally run clinical trials. The Committee however considered that the impact of this may be greater in this instance, as many of the relevant eribulin studies were undertaken in Japan. The Committee noted that this is a particularly homogeneous population, and that this presented greater uncertainty in its generalisability to the New Zealand population.

5.4.7. The Committee acknowledged the role of patient support and advocacy groups, and considered there to be great value from BCAC engaging in Pharmac processes.

Health need

5.5. The Committee reiterated the unmet health need of people with advanced or metastatic breast cancer, particularly for Māori and Pacific peoples. The Committee considered that part of the cause for them experiencing worse outcomes is due to the stage of disease at diagnosis, and that it was more important to ensure that the health system provides equitable access to screening.

5.6. The Committee noted that the unmet health need for people with triple negative breast cancer (TNBC) was exacerbated by the lesser availability of treatments for this population group.

Health benefits

5.7. The Committee noted that it previously reviewed 14 studies supporting the efficacy of eribulin. The Committee noted that it had considered the key evidence (EMBRACE trial) for benefit of eribulin in locally advanced or metastatic breast cancer was of medium strength and quality (Yuan et al. Eur J Cancer. 2019;112:57-65). However, on balance, the totality of all of the evidence supporting eribulin in this setting was considered low quality.

5.8. The Committee noted its previous consideration regarding what it had regarded was limited evidence of benefit for people with TNBC or human epidermal growth factor receptor 2 (HER2) -negative disease. The Committee noted that the consideration had been based on the Committee's assessment of what was a wide base of evidence and had included its critical appraisal of the key pivotal clinical trials supporting the use of eribulin. The Committee noted that there was confounding in many of the studies from including patients with HER2-positive breast cancer, that there was limited evidence of improvements in outcomes, concerns regarding the safety profile of eribulin compared to other treatments for the TNBC indication, and that many of the trials appeared imbalanced by the baseline disease burden being greater in the comparator arms. The Committee noted that the evidence supporting its use in TNBC breast cancer came primarily from a subgroup of the intent-to-treat population of studies 301 and 305, supported by what were post-hoc analyses, and therefore this evidence needed to be interpreted with considerable caution.

5.9. The Committee noted the additional studies provided by BCAC and the supplier to support the use of eribulin in people with locally advanced or metastatic breast cancer:

- Maeda S, et al. Breast 2017;32:66-72
- Watanabe J, et al. Invest New Drugs. 2017;35(6):791-9
- Kikuchi Y, et al. Asia Pac J Clin Oncol. 2018;14(5):e231-e237
- Kimura K, et al. Cancer Chemother Pharmacol. 2018;81(5):923-33
- Inoue K, et al. Invest New Drugs. 2020;38(5):1540-9
- Barni S, et al. Future Oncol. 2019;15(1):33-44
- Lorusso V, et al. Future Oncol. 2017;13(11):971-8
- Adamo V, et al. Ther Adv Med Oncol. 2019;11:1758835919895755
- Krasniqi E, et al. Int J Med Sci. 2021;18(10):2245-50
- Garrone O, et al. Springerplus. 2016;5:59
- Pedersini R, et al. Oncology. 2018;94((Suppl 1)):10-5
- Aftimos P, et al. Eur J Cancer. 2016;60:117-24
- Sabatier R, et al. Cancer Res Treat. 2018;50(4):1226-37
- Mougalian SS, et al. Cancer Med. 2018;7(9):4371-78
- Mougalian SS, et al. Adv Ther. 2021;38(5):2213-25
- Cortes J and Twelves C. Breast J. 2020;26(7):1347-51
- Twelves C, et al. Breast Cancer (Auckl). 2016;10:77-84
- Pivot X, et al. Ann Oncol. 2016;27(8):1525-31
- Jafri M, et al. Oncology. 2022;100(12):666-73
- Chan A, et al. Asia Pac J Clin Oncol. 2022;18(3):201-8

5.10. The Committee considered that the additional evidence provided by BCAC and the supplier reinforced its considerations provided at the previous meeting.

5.10.1. The Committee noted that many of the trials did not include comparators, many of which were observational non-experimental studies or retrospective post-hoc pooled analyses which provided less robust evidence of benefit in patients with HER2-negative or TNBC.

5.10.2. The Committee noted that there was variability in the levels of pre-treatment across these studies and uncertainty in the efficacy of eribulin for those people with brain metastases.

5.10.3. The Committee noted that most studies were performed in Japan, and that the generalisability to the NZ population was uncertain, given the comparative homogeneity of the Japanese population.

5.10.4. The Committee noted that many of these additional studies reported on radiologic endpoints reflecting response to treatment, rather than clinical endpoints.

5.10.5. The Committee reiterated that the evidence supporting the benefit for people with TNBC originated from post hoc analyses. The Committee did, acknowledge that there may be improvements in survival for this subgroup, but the level of benefit was uncertain.

5.10.6. The Committee noted that one of the two originally reviewed randomised studies did report a small but statistically significant benefit in overall survival. The Committee considered that most of these additional trials reinforced the small improvement in long term outcomes from treatment. The Committee considered that there was uncertainty regarding the safety profile of eribulin compared to standard of care, but considered eribulin's toxicity profile was manageable.

Closing

5.11. The Committee noted that the primary focus of its November 2022 review was the relevant randomised clinical trials, which the Committee had considered to be of medium quality and strength. The Committee considered, however, that the majority of the supporting evidence reviewed to date (randomised controlled trials, cohort studies, and the other evidence cited above), supporting the efficacy and safety of eribulin, was overall of low quality (given in particular the preponderance of non-randomised evidence presented), as was therefore the summative quality overall.

5.12. The Committee acknowledged that lower levels of evidence (eg observational or cohort study evidence, at times labelled as 'real-world' evidence) are being increasingly promoted to, and accepted by, other jurisdictions as sufficient to make health funding decisions. The Committee noted this was likely because at times 'real world' evidence may be more directly relevant to funding settings than available randomised trial evidence, and that there were new methodologies to support considering such lower-level evidence. However, the Committee emphasised the need for evidence to be as robust (internally valid) as possible.

5.13. The Committee reiterated its previous recommendations regarding the use of eribulin for this patient population, but also noted the request of the applicant for this to be reviewed by the Cancer Treatments Advisory Committee (CTAC). The Committee considered that if this were to occur, it would be useful for CTAC to consider eribulin's potential benefit in the subgroup of those people with TNBC, when compared with funded alternatives, including integrating any evidence of efficacy specific to that tumour type.

6. Palivizumab – extension of funding for RSV

Application

6.1. The Advisory Committee reviewed the application for continued funding of palivizumab in the prevention of respiratory syncytial virus (RSV).

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

Recommendation

6.3. The Advisory Committee **recommended** that funding be continued for palivizumab in the prevention of RSV, with a high priority, subject to the following Special Authority criteria:

> Initial application — (RSV prophylaxis) only from a paediatrician. Approvals valid for 6 months for applications meeting the following criteria:
> Either:
> 1 Child was born in the last 2 years and has severe lung, airway, neurological or neuromuscular disease that requires ongoing, life-sustaining ventilation/respiratory support in the community; or
> 2 Both:
> 2.1 Infant was born in the last 12 months; and
> 2.2 Any of the following:
> 2.2.1 Patient was born at less than 28 weeks gestation; or
> 2.2.2 Both:
> 2.2.2.1 Patient was born at less than 32 weeks gestation; and
> 2.2.2.2 Either:
> 2.2.2.2.1 Patient has chronic lung disease; or
> 2.2.2.2.2 Patient is Māori or any Pacific ethnicity; or
> 2.2.3 Both:
> 2.2.3.1 Patient has haemodynamically significant heart disease; and
> 2.2.3.2 Any of the following:
> 2.2.3.2.1 Patient has unoperated simple congenital heart disease with significant left to right shunt (see note a); or
> 2.2.3.2.2 Patient has unoperated or surgically palliated complex congenital heart disease; or
> 2.2.3.2.3 Patient has severe pulmonary hypertension (see note b); or
> 2.2.3.2.4 Patient has moderate or severe LV failure (see note c).
>
> Notes:
> a) Patient requires/will require heart failure medication, and/or patient has significant pulmonary hypertension, and/or patient all require surgical palliation/definitive repair within the next 3 months.
> b) Mean pulmonary artery pressure more than 25 mmHg.
> c) LV Ejection Fraction less than 40%.
>
> Renewal — (RSV prophylaxis) only from a paediatrician. Approvals valid for 6 months where patient still meets initial criteria.

6.4. The Advisory Committee considered the following in making this recommendation:

- The currently funded population are already vulnerable and they and their caregivers/whānau require a high level of health system care, engagement, and support.
- RSV disproportionately affects premature infants in their first year of life. Māori are overrepresented both among infants born prematurely and among those infants with severe RSV disease requiring intensive care treatment.
- Hospitalisation from RSV is independently associated with ethnicity, and Māori and Pacific infants are more likely to be hospitalised than infants of other ethnicities.
- In observational data supplied from Waikato, Capital & Coast, and Counties Manukau regions, no infant admitted to hospital or intensive care unit (ICU) for RSV had received prior palivizumab.

- The evidence for benefit of prophylactic palivizumab was reduction in hospitalisations for RSV and thus reduced the burden on the health system.

- The estimated immunisation uptake of 45% of the eligible population is lower than expected and would require substantial engagement with community providers to improve uptake if funding were to be extended.

Discussion

Māori impact

6.5. The Committee discussed the impact of funding palivizumab for the prevention of RSV on Māori health areas of focus and Māori health outcomes. The Committee noted its previous advice that RSV disproportionately affects premature infants in their first year of life, with Māori infants more likely to be born premature. The Committee also considered that Māori are overrepresented in those infants with severe RSV disease requiring intensive care treatment.

6.6. The Committee noted evidence reporting ethnicity as an independent risk factor for hospitalisation (Grimwood et al. Epidemiol Infect. 2008;136:1333-41; Prasad et al. Epidemiol Infect. 2019;147:e246). The Committee noted that Grimwood et al. used multiple variable regression analysis accounting for gestation, birthweight, socioeconomic status (as NZDep2001 score), and ethnicity. The Committee noted that it was reported that Māori infants are more likely to be hospitalised with RSV than non-Māori and that this association was independent of gestation, birthweight and socioeconomic status (adjusted risk ratio (aRR) 3.64; 95%CI: 2.27–5.85) (Grimwood et al.).

Background

6.7. The Committee noted its previous advice from February 2022 recommending that palivizumab be funded for the 2022 and 2023 RSV seasons for prophylaxis of children under the age of 12 months who are at high risk of developing RSV disease. The Committee noted that this recommendation was made in the context of the 2021 RSV season, which had significantly higher than expected paediatric hospital and ICU admissions with RSV disease over the season, and the likelihood of this occurring again in the 2022/23 season with the border re-opening as COVID-19 public health restrictions were eased.

6.8. In particular, the Committee noted that RSV disproportionately affects premature infants, in their first year of life, with those who are Māori, Pacific, or living in areas with low socioeconomic privilege (NZDEP deprivation index 8-10) carrying a higher risk compared to the general population, since they are more likely to be born premature The Committee considered that these groups are also overrepresented in intensive care, suggesting a more severe form of disease. The Committee considered that those who receive poor antenatal care are also more likely to have a premature birth. The Committee considered that this inequitably burdens Māori, Pacific peoples and those living in areas associated with low socioeconomic status.

6.9. The Committee noted evidence reporting ethnicity as an independent risk factor for hospitalisation (Grimwood et al. Epidemiol Infect. 2008;136:1333-41; Prasad et al. Epidemiol Infect. 2019;147:e246). The Committee noted that Grimwood et al. used multiple variable regression analysis that accounted for gestation, birthweight, socioeconomic status (as NZDep2001 score), and ethnicity. The Committee noted that it was reported that Māori infants are more likely to be hospitalised with RSV than non-Māori infants (aRR 3.64; 95%CI: 2.27–5.85). The Committee noted that it was reported that Pacific infants are more likely to be hospitalised with RSV than non-Pacific infants (aRR 3.60; 95%CI: 2.14–6.06) (Grimwood et al.). The Committee noted that these

associations were independent of gestation, birthweight and socioeconomic status (Grimwood et al.).

6.10. The Committee considered the reduction in hospitalisations for RSV gained from palivizumab would benefit the health system, given the expected burden of COVID-19 as restrictions eased.

6.11. Additionally, in April 2022, the Respiratory Advisory Committee reviewed PTAC's advice, and considered that children over 12 months who were still dependent on ventilation/respiratory support in the community were at very high risk of severe RSV-related illness, and recommended these children also be considered in the eligibility criteria.

Health need

6.12. The Committee considered that the currently funded population is already vulnerable and required a high level of health system engagement and support. The Committee considered that for children eligible for funded palivizumab that the short-term annual baseline risk of hospitalisation (without any prior palivizumab treatment) is 23%, consistent with historic estimates for New Zealand (Vogel et al. J Paediatr Child Health. 2002;38(4):352-7).

6.13. The Committee considered that children over 2 years of age are less likely to have severe RSV requiring hospitalisation, as anatomically their bronchioles are larger and they are therefore less likely to develop physiological/inflammatory respiratory tract complications that result in hospitalisation.

6.14. The Committee considered that the health need of the individual and the environment was dependent on the prevalence of the virus in the environment. The Committee considered that the 2022 season of RSV was not atypical (in contrast with the previous 2021 atypical experience with much higher incidence rates) and that concurrently the effect of COVID-19 on hospitals is decreasing.

6.15. The Committee considered that the health need of groups inequitably affected by RSV remained the same as advised in February 2022. The Committee considered that the implementation of the immunisation programme was the way to appropriately address the inequities. The Committee considered that inclusion of other groups such as those with Down syndrome, those who are immunocompromised or with chronic neuromuscular disorders were not appropriate as there was currently insufficient evidence to support immunisation.

6.16. The Committee considered that COVID-19 population level disease control measures were unlikely to affect the health need of those eligible for funding, as COVID-19 population preventive measures have been scaled down extensively in most countries, including New Zealand and COVID-19 is generally a considerably less serious disease in children. The Committee noted that the predicted numbers of RSV cases did not eventuate in association with the opening of the borders in 2022, and the rest of the world has not recently experienced atypical RSV seasons.

6.17. The Committee considered that the concern about COVID-19 and RSV co-infection and the effect on eligible children did not eventuate in 2022, and considered this to likely continue to be the case for the 2023 season.

Health benefit

6.18. The Committee considered the evidence for benefit had not changed since its last review in February 2022. The Committee considered the evidence for benefit of prophylactic palivizumab was reduction in hospitalisations which would reduce the burden on the

health system. The Committee noted reduced risks of hospitalisation associated with palivizumab prophylaxis in the Impact-RSV trial of 39% in children with chronic lung disease (CLD) and 78% in those without CLD (Impact-RSV Study Group. Pediatrics. 1998;102:531-7; Schmidt et al. Health Economics Review, 2017;7(47); Wang et al. Health Technol Assess. 2011;15(5):iii-iv,1-124).

6.19. The Committee considered that other outcomes such as reductions in mortality or long-term respiratory sequelae were supported by evidence of poor quality and weak strength, and therefore it was not appropriate to include these outcomes in economic modelling. The Committee considered there was no evidence of long-term benefits.

6.20. The Committee considered that evidence to support a quality-of-life benefit for individual children or families of children given palivizumab is lacking empirically, but considered that hospitalisation of a child would have a negative impact on individuals and family/ whānau.

6.21. The Committee considered the impact having a child with RSV in paediatric ICU (PICU) might have on the risk to other critically ill children who would need be protected against RSV. The Committee considered that such measures include isolating vulnerable children who had undergone transplant surgery, and having a specific room for children with bronchiolitis to avoid single room barrier nursing. The Committee considered that, although not yet routinely implemented for RSV, appropriate vaccination for other infectious diseases is currently used to protect vulnerable children within PICU.

6.22. The Committee considered that children who are treated with palivizumab still have the same risk of hospitalisation from other respiratory infections. The Committee considered that the palivizumab-eligible group acquiring severe RSV requiring hospitalisation will require admission for a duration of 10 days on average, and would often require ICU admission. The Committee considered that others that were not eligible for palivizumab, but severe enough to require hospitalisation, would require an average of 3-days admission to hospital.

6.23. The Committee considered that infants' health-related quality of life would be poor during acute RSV illness severe enough to require hospitalisation. The Committee considered that disease severe enough to require PICU admission and care would be particularly decremental to the health-related quality of life of the infant while in PICU. The Committee considered that there would be further quality of life loss before and during convalescence, after acute illness.

6.24. The Committee considered there would also be short-term RSV-related morbidity in those very high-risk infants who were unwell but did not require inpatient hospitalisation.

6.25. The Committee noted its previous advice regarding implementation of this programme, in particular, substantial engagement with the relevant clinical teams (neonatal ICU (NICU), PICU, and paediatric cardiology, respiratory, and infectious diseases teams) and community health providers (Māori and Pacific health providers, rural health providers), and resolution of important logistical challenges regarding palivizumab's distribution, administration, vial sharing, and identification of eligible children.

6.26. The Committee considered the data provided from Te Whatu Ora regions was not uniform or complete, and that uptake of palivizumab in eligible children could be calculated from data from one region only. The Committee considered that the estimated uptake of 45% of the eligible population was lower than expected and would require more engagement with community providers to improve this if funded for the longer term. The Committee noted that as infrastructure is already in place uptake should be ~80% if implemented appropriately.

6.27. The Committee considered that different regions had implemented the palivizumab prophylaxis programme to varying degrees of success. The Committee noted from observational data supplied by Waikato, Capital & Coast, and Counties Manukau regions that none of the infants that were recorded as admitted to hospital or ICU had received prior palivizumab. With this, members noted specifically that:

6.27.1. in the Waikato region during 2022, of 68 or 71 infants eligible for palivizumab (counts not fully determined at the time of the meeting), 31 (44% or 46% of all eligible) were given palivizumab, of whom none required hospitalisation for RSV disease; this compared with the 37 (54-56%) who were not given palivizumab, of whom 8 were hospitalised with RSV disease (20-22% of those eligible but not given palivizumab)

6.27.2. for Wellington city during 2022, of 21 infants that met criteria for and were given palivizumab (where the prevalence of eligible children actually given palivizumab was not provided), none were subsequently diagnosed with or admitted to hospital for RSV infection

6.27.3. in the Counties Manukau region for 2021 and 2022, no children who received palivizumab were admitted to hospital subsequently with RSV positive lower respiratory tract infection.

6.28. Members considered that there was little awareness of this programme with community providers. The Committee considered there are already vaccination networks in place that could be used to help administer this programme through the community.

Cost and savings

6.29. The Committee considered the cost of retrieval of critically ill children from regions in New Zealand on the health system to be significant, with the return trip of a fixed wing aeroplane or helicopter, pilot and clinical staff, aviation fuel, air ambulance service overheads required to travel to and from Starship PICU for retrieval at what members considered might cost up to $30,000-50,000 per retrieval episode for distant regions. The Committee understood that up to six retrievals may occur over weekend periods during RSV season via fixed wing aeroplane, helicopter or road ambulance depending on region and resources available.

6.30. The Committee noted that implementation costs were not included in Pharmac's preliminary analysis, such as family travel time and costs to receive palivizumab (monthly for 6 months over the RSV season), after hours GP costs, and transportation – these costs would be potentially significant and unaffordable for family/whanau of high-risk children.

6.31. The Committee considered that prior to hospitalisation, illness would worsen over 2 to 3 days, and members estimated post-hospitalisation convalescence back to usual health of 6 weeks. The Committee considered that the usual time period of an acute RSV infection is 7 to 10 days, with most children experiencing this respiratory illness during their first year of their life.

6.32. The Committee considered that reduction in GP and emergency department (ED) visits would be likely for high-risk children with RSV who are not hospitalised. The Committee considered that in general, those under 2 years old would be seen by a GP 2 to 4 times per episode in order to avoid urgent care or ED attendance, however those children eligible for palivizumab who are acutely unwell will likely present to urgent care or ED, as they are particularly vulnerable. The Committee considered that EDs have seen an increased workload over the last three years.

Funding criteria

6.33. The Committee considered the current Special Authority criteria were appropriate.

Summary for assessment

6.34. The Advisory 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 Advisory 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 who were either, • Born at less than 28 weeks gestation, or • Born 29 to 32 weeks gestation and have chronic lung disease, or • Born 29 to 32 weeks gestation and is Māori or Pacific, or • Infants who have haemodynamically significant heart disease. OR Child was born in the last 2 years who has severe lung, airway, neurological or neuromuscular disease that requires ongoing, life-sustaining ventilation/respiratory support in the community.
Intervention	Palivizumab 15mg/kg given monthly via IM injection. Based on Pharmac data, the average number of doses per infant each RSV season is 4.3
Comparator(s) (NZ context)	Best supportive care
Outcome(s)	• Reduced hospitalisations • Reduced number of ED and GP visits • Improved short-term health-related quality of life among infants who avoid hospitalisation
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 target 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.	

7. Fixed-duration ibrutinib plus venetoclax - previously untreated Chronic Lymphocytic Leukaemia (CLL) or Small Lymphocytic Leukaemia (SLL) patients without del(17p)/TP53 mutation

Application

7.1. The Advisory Committee reviewed the application for fixed-duration ibrutinib plus venetoclax (I+V) for the treatment of previously untreated Chronic Lymphocytic Leukaemia (CLL) or Small Lymphocytic Leukaemia (SLL) without del(17p)/TP53.

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

Recommendation

7.3. The Advisory Committee **recommended** that fixed duration ibrutinib plus venetoclax (I+V) for the treatment of previously untreated Chronic Lymphocytic Leukaemia (CLL) or Small Lymphocytic Leukaemia (SLL) without del(17p)/TP53 be funded with a **high priorit**y for individuals who are not eligible for chemoimmunotherapy.

7.4. The Advisory Committee **recommended** that fixed duration ibrutinib plus venetoclax (I+V) for the treatment of previously untreated Chronic Lymphocytic Leukaemia (CLL) or Small Lymphocytic Leukaemia (SLL) without del(17p)/TP53 be funded with a **medium** for individuals who are eligible for chemoimmunotherapy.

7.5. The Committee considered that both recommendations should be subject to the following Special Authority criteria:

VENETOCLAX
Initial application (untreated chronic lymphocytic leukaemia without 17p deletion or TP53 mutation) - only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months.
All of the following:
1. Person has previously untreated chronic lymphocytic leukaemia; and
2. There is documentation confirming the person does not have 17p deletion or TP53 mutation
3. Venetoclax is to be administered in combination with ibrutinib, beginning at cycle four of ibrutinib therapy.

Renewal application (untreated chronic lymphocytic leukaemia without 17p deletion or TP53 mutation) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. No evidence of clinical disease progression; and
2. The treatment remains appropriate and the person is benefiting from treatment; and
3. Venetoclax is to be administered in combination with ibrutinib; and
4. Venetoclax is to be discontinued after a maximum of 12 (28 day) cycles

IBRUTINIB
Initial application (untreated chronic lymphocytic leukaemia without 17p deletion or TP53 mutation) - only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months.
All of the following:
1. Person has previously untreated CLL; and
2. There is documentation confirming the person does not have 17p deletion or TP53 mutation; and
3. Ibrutinib is to be administered at a maximum dose of 420 mg daily for 3 (28 day) cycles

Renewal application (untreated chronic lymphocytic leukaemia without 17p deletion or TP53 mutation) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
Both:
1. No evidence of clinical disease progression; and
2. The treatment remains appropriate and the person is benefiting from treatment; and
3. Ibrutinib to be administered in combination with venetoclax; and
4. Ibrutinib is to be discontinued after a maximum of 15 (28 day cycles) of treatment.

7.6. In making this recommendation, the Advisory Committee considered:

7.6.1. Despite the use of other treatment regimens, and improved overall survival rates over time, individuals with CLL/SLL still suffer premature death and reduced health-related quality of life.

7.6.2. That current evidence shows that whilst not definitively proven, it is highly likely that ibrutinib + venetoclax is superior to fludarabine + cyclophosphamide + rituximab as first line treatment of CLL/SLL in individuals for whom chemoimmunotherapy is suitable. For individuals for whom chemoimmunotherapy is unsuitable there is high

quality evidence of a benefit of ibrutinib + venetoclax compared with current standard of care.

7.6.3. That ibrutinib with venetoclax has a more favourable suitability profile compared to currently available treatment options which require intravenous infusion, due to its oral administration.

7.6.4. If ibrutinib with venetoclax were funded for this indication, there would be decreased demand for infusion services which would be associated with health sector cost savings.

7.6.5. If ibrutinib with venetoclax were funded for this indication, it may be used in up to 90% of eligible individuals, as it was likely to be a popular regimen.

Discussion

Māori impact

7.7. The Committee discussed the impact of funding fixed duration ibrutinib plus venetoclax for the treatment of previously untreated Chronic Lymphocytic Leukaemia (CLL) or Small Lymphocytic Leukaemia (SLL) on Māori health areas of focus and Māori health outcomes. The Committee noted that CLL/SLL is not specifically a Pharmac Hauora Arotahi Māori health area of focus. The Committee considered that there is no direct evidence to suggest that incidence of CLL in Māori is any greater than that of other New Zealand populations.

Background

7.8. The Committee noted previous considerations for ibrutinib and venetoclax with Obinutuzumab by PTAC in November 2015, August 2016, November 2016, February 2017, and by CTAC (previously CaTSoP) in May 2016, September 2016, September 2018, July 2019, and July 2020.

Health need

7.9. The Committee noted that CLL is a slow-growing type of non-Hodgkins lymphoma in which immature lymphocytes (white blood cells) are found in the blood and bone marrow and/or the lymph nodes. The Committee noted that CLL and SLL are the same disease, but in CLL cancer cells are found mostly in the blood and bone marrow, and in SLL cancer cells are found mostly in the lymph nodes.

7.10. The Committee considered that reasons to treat CLL/SLL include 'B symptoms' (weight loss of >10% of body weight in the previous 6 months, severe fatigue, fevers >38°C for at least 2 weeks without evidence of infection, drenching night sweats for more than a month without evidence of infection), evidence of progressive bone marrow failure, massive or symptomatic splenomegaly, massive lymph nodes or clusters of nodes (>10 cm) or progressive or symptomatic lymphadenopathy, Autoimmune Haemolytic Anaemia and/or Immune Thrombocytopenic Purpura that is poorly responsive to steroids or other standard therapy, and rising ALC with an increase of more than 50% over a 2-month period or a lymphocyte doubling time (LDT) <6 months.

7.11. The Committee noted that there is a differential loss of life expectancy correlated to the age at which an individual is diagnosed with SLL/CLL, and the loss of life years has decreased due to new treatments being introduced over the last 30 years. The Committee noted that a person diagnosed at 50 years would have been expected to lose approximately 20 life years in 1989 compared to approximately 10 years in 2018. The Committee also noted that the older a person is at diagnosis, the less life-years they are likely to lose, with less than 5 years lost if diagnosed at 80 years.

Health benefit

7.12. The Committee noted that venetoclax is an orally bioavailable small-molecule inhibitor of BCL-2, an anti-apoptotic protein that is over-expressed in CLL cells. Venetoclax binds directly to BCL-2, displacing pro-apoptotic proteins resulting in the restoration of apoptotic processes, and ibrutinib is a Bruton's tyrosine kinase inhibitor (BTKi), a kinase downstream of the B-cell receptor that is critical for B-cell survival and proliferation. Ibrutinib binds to Bruton's tyrosine kinase with high affinity, leading to inhibition of B-cell receptor signalling, decreased B-cell activation and induction of apoptosis.

7.13. The Committee noted that both venetoclax and ibrutinib have been shown to be of use in first and subsequent lines of treatment for CLL/SLL, but the proposed intervention is to use the combination as first line treatment in individuals without high risk features (unmutated IGHV, Del [17p], Del [11q] and other TP53 mutations), for individuals that are both fit and unfit for chemoimmunotherapy (CIT), for a fixed duration (15 months in total).

7.14. The Committee noted that the comparator for fixed duration ibrutinib + venetoclax (I+V) in those suitable for CIT is either; Fludarabine + Cyclophosphamide + Rituximab (FCR) or Bendamustine + Rituximab (BR), depending on an individual's ability to withstand FCR which has a worse adverse event profile compared with BR. The Committee noted that the comparator for fixed duration ibrutinib + venetoclax (I+V) in those for whom CIT is unsuitable (due to cumulative illness rating [CIR] of >6 or GFR of < 70ml/min) is Obinutuzumab + Chlorambucil (OC).

7.15. The Committee considered relevant outcomes for evidence of efficacy of fixed duration I+V include undetectable minimal residual disease (uMRD), progression free survival (PFS), overall survival (OS), and health-related quality of life (HRQoL).

7.16. The Committee reviewed results from the GLOW trial (Kater et al. NEJM Evid. 2022;1(7)); a phase III randomised open-label trial in individuals with previously untreated CLL/SLL who would be considered unfit for treatment with fludarabine based CIT (CIRS>6), who were treated with I+V or Chlorambucil-obinutuzumab. The Committee considered uMRD superior in the I+V arm, which was achieved in 55.7% of the I+V group vs 21.0% of the C+O arm at the time or primary analysis. (P<0.001), and the proportion of patients with sustained uMRD in peripheral blood from 3 to 12 months after end of treatment was 84.5% I+V arm and 29.3% C+O arm. The Committee noted at median follow-up of 27.7 months, 22 PFS events in I+V arm and 67 occurred in C+O arm (hazard ratio [HR] 0.216; 95% CI 0.131 to 0.357; P<0.001) and considered PFS superior in the I+V arm (Kater et al. NEJM Evid. 2022;1(7). The Committee noted that improved overall survival was seen in the I+V group at the 46-month follow up: 87.5% I+V vs 77.6% C+O (HR 0.487; 95% CI 0.262-0.907; nominal P=0.0205) (Niemann et al. ASH 2022.). The Committee noted the HRQoL was incomplete, and not formally reported from the study.

7.17. The Committee considered results from the GLOW trial as high-quality evidence of a benefit of I+V compared with the current standard of care (OC) relating to uMRD, PFS and OS in individuals who are unsuitable for CIT. The Committee noted that HRQoL data is immature but may affect the cost-utility analysis.

7.18. The Committee noted that no cases of Tumour Lysis Syndrome occurred in the I+V arm of the GLOW study. Cumulative literature demonstrates that ibrutinib induction over 3 months successfully debulks the disease and reduces the risk of TLS considerably.

7.19. The Committee noted there is limited head-to-head data comparing I+V to either FCR or BR for CLL in individuals suitable for CIT therapy. The Committee noted that FCR and BR were compared head-to-head in the CLL10 trial, which showed median PFS was superior with FCR (57.6 months versus 42.3 months), but this did not translate into an OS benefit, which was possibly confounded by the fact that 30% of BR patients received subsequent FCR. The Committee noted that HRQoL was measured and was not different

between the groups. The Committee did not consider the populations in the CLL10 trial to be directly comparable to the CAPTIVATE population, as the age range was greater in CLL10.

7.20. The Committee reviewed results relating to the Fixed Dose (FD) arm of the CAPTIVATE trial, where 15 months of I+V was given to individuals with previously untreated CLL/SLL who would be considered suitable for CIT (Tam et al. Blood. 2022;139(22):3278-89). The Committee noted that several of the individuals included in the study were from New Zealand, and thus considered the results relevant to the New Zealand population. The Committee considered I+V showed efficacy in uMRD rates across individuals with del(17p) and/or mutated TP53: 81% (95% CI, 67-96) in peripheral blood and 41% (95% CI, 22-59) in bone marrow, and without del(17p): 76% (95% CI, 69-84) in peripheral blood and 62% (95% CI, 54-70) in bone marrow. The Committee noted that the 3-year follow up showed PFS rates of 80% in the del(17p) and/or mutated TP53 group, and 88% in the non-mutated group (Wierda et al. ASCO 2022., Moreno et al. EHA 2022.). The Committee considered that the CAPTIVATE trial showed good quality evidence for efficacy of fixed duration I+V in individuals with and without del(17p) and/or mutated TP53, but stronger efficacy in the non-mutated group.

7.21. The Committee reviewed results from the E1912 trial ClinicalTrials.gov Identifier: NCT02048813): an open-label, randomised phase III trial investigating ibrutinib and rituximab (six cycles) versus fludarabine phosphate, cyclophosphamide, and rituximab (FCR) in treating individuals (354 in the ibrutinib-rituximab group, and 175 in the CITgroup) with untreated CLL/SLL. The Committee noted at a median follow-up of 33.6 months, the results for PFS favoured ibrutinib-rituximab over CIT (89.4% vs. 72.9% at 3 years; HR for progression or death 0.35; 95% CI 0.22 to 0.56; P<0.001). OS also favoured ibrutinib-rituximab over CIT(98.8% vs. 91.5% at 3 years; HR for death 0.17; 95% CI 0.05 to 0.54; P<0.001) (Shanafelt et al. N Engl J med. 2019;381:432-43), and at 5.8 year median follow-up, the 5-year progression free survival rate for ibrutinib-rituximab was 78% overall versus 51% with FCR (HR 037; 95% CI 0.27-0.51; P < 0.0001). For OS, 5-year rates were 95% in the ibrutinib-rituximab group, versus 89% in the FCR group (HR 0.47; 95% CI 0.25-0.89; P = 0.018) (Shanafelt et al. Blood. 2022;140:112-20). The Committee noted that the inclusion criteria for E1912 were similar to those used in CAPTIVATE, and the trial was reviewed because the control arm was then utilised in the indirect treatment comparison reviewed below.

7.22. The Committee reviewed an indirect treatment comparison (ITC) study of fixed-duration I + V vs FCR as first line treatment for CLL (Barrientos et al. Hemasphere. 2022; 6(Suppl): 1758-9). The study compared previously untreated CLL or SLL aged ≤70 y who were treated with I+V in the FD cohort of CAPTIVATE to patients treated with FCR in E1912. Adjusted treatment effects for PFS, OS, and ORR were estimated by inverse probability of treatment weighting (IPTW) using propensity scores. After IPTW, PFS was improved with I+V relative to FCR (hazard ratio [HR] 0.42; 95% CI 0.25-0.71), as was OS (HR 0.19; 95% CI 0.05-0.77). The Committee considered the ITC was of high quality and likely provides the best current evidence of I+V vs FCR in for first line CLL.

7.23. The Committee noted results of the currently active ERADIC trial, a head-to-head, Phase II comparison of FCR with I+V in individuals with CLL, excluding those with del(17p) or TP53 mutation but including individuals with the with unmutated IGHV, del (11q) or a complex karyotype ClinicalTrials,gov Identifier:NCT04010968. The Committee noted the 9-month interim data showed the level of uMRD is currently lower in the I+V group than the FCR group. The Committee noted these data are currently immature and may change when final data is published.

7.24. The Committee considered that the evidence outlined above showed high quality evidence of benefit of I+V compared to current standard of care for individuals for whom CIT is unsuitable. For individuals for whom CIT is suitable, while not definitively proven, it is highly likely that I+V is superior to FCR as first line treatment of CLL/SLL.

7.25. The Committee considered that retreatment with venetoclax may be suitable for R/R CLL/SLL in the future, but considered that current evidence is poor quality (Thompson et al. Blood Adv. 2022;6:4553-7), and further, good quality evidence was required to support its repeated use therefore did not recommend changing the special authority criteria at this stage.

Suitability

7.26. The Committee considered that ibrutinib with venetoclax has a more favourable suitability profile compared to currently available treatment options due to its all-oral administration. The Committee considered that this means that individuals receiving this treatment will not need to travel as frequently to receive treatment.

Cost and savings

7.27. The Committee noted that currently all first-line treatment options for CLL without del(17p)/TP35 mutation require intravenously administered infusions, in a clinical facility offering a higher level of treatment support (such as a hospital or infusion centre). The Committee noted that if ibrutinib with venetoclax were funded for this indication, decreased demand for infusion services would occur due to the medications' oral administration.

7.28. The Committee considered the relative proportions of FCR, BR and OC in the comparator (60:20:20) and intervention (20:5:5:70 with I+V) proposed by the supplier to be reasonable, however considered I+V may end up capturing closer to 90% of patients, as it was likely to be a popular regimen. The Committee considered this would be the case even if venetoclax retreatment was not an option for these patients.

Summary for assessment

7.29. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for ibrutinib with venetoclax if it were to be funded in New Zealand for previously untreated CLL/SLL. 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 Advisory 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	People with previously untreated CLL/SLL without del(17p) / TP53 mutation considered **unfit** for treatment with fludarabine or bendamustine based chemo-immunotherapy. **(20%)**	People with previously untreated CLL/SLL without del(17p) / TP53 mutation who would otherwise be considered **fit** for treatment with fludarabine or bendamustine based chemo-immunotherapy. **(80%)**
Intervention	Fixed duration ibrutinib + venetoclax (I+V) (15 cycles in total, fixed duration therapy) Venetoclax: Administered orally once daily with 5-week dose ramp up, added to ongoing ibrutinib therapy starting at Cycle 4 and continued for 12 cycles. On progression treated with: 1. OC 2. Chlorambucil monotherapy	Fixed duration ibrutinib + venetoclax (I+V) (15 cycles in total, fixed duration therapy) Venetoclax: Administered orally once daily with 5-week dose ramp up, added to ongoing ibrutinib therapy starting at Cycle 4 and continued for 12 cycles. On progression treated with: 1. FCR / BR 2. OC 3. FCR/ BR retreatment
Comparator	Obinutuzumab plus chlorambucil (OC) On progression treated with: 1. Venetoclax + rituximab 2. Ibrutinib monotherapy Chlorambucil monotherapy	Fludarabine, cyclophosphamide, and rituximab (FCR) OR Bendamustine + Rituximab (BR) On progression treated with: 1. Venetoclax + rituximab 2. Ibrutinib monotherapy 3. OC
Outcomes	Longer PFS per GLOW trial (42-mo PFS I+V 74.6% vs OC 24.8%) and longer OS (42-mo OS I+V 87.5% vs OC 77.6%)	Longer PFS and OS via indirect comparison of CAPTIVATE and the E1912trial

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 target 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.

OC: Obinutuzumab plus chlorambucil; V+R: Venetoclax plus rituximab

8. Empagliflozin for the treatment of chronic heart failure with a New York Heart Association functional classification of class II to IV and left ventricular ejection fraction greater than 40%

Application

8.1. 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 preserved (HFpEF) or mildly reduced ejection fraction (HFmrEF), as an add-on to optimal standard CHF treatments, for individuals with NYHA class II-IV and left ventricular ejection fraction (LVEF) > 40%.

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

Recommendation

8.3. The Committee **recommended** that empagliflozin for the treatment of HFpEF/HFmrEF, as an add-on to optimal standard CHF treatments, in individuals with NYHA class II-IV and LVEF >40% be **declined**. In making this recommendation, the Committee considered:

8.3.1. The high health need of individuals with HFpEF/HFmrEF and the lack of HFpEF/HFmrEF specific-avaliable therapies, and

8.3.2. The limited evidence that empagliflozin provides a health benefit for individuals with HFpEF/HFmrEF other than reduced frequency of hospitalisations with symptomatic heart failure, above currently funded treatments.

Discussion

Māori impact

8.4. The Committee noted that heart failure falls under one of Pharmac's Hauora Arotahi (Māori health areas of focus): *Manawa Ora - Heart health, high blood pressure and stroke*. The Committee noted that Māori are on average 10 to 15 years younger at age of diagnosis with heart failure, compared to non-Māori. The Committee also noted that Māori with heart failure have higher hospitalisation rates (four times as likely as non-Māori) and experience reduced survival compared to non-Māori.

8.5. The Committee noted that Māori with heart failure (HF) experience reduced access to optimal care compared to non-Māori due to barriers to specialist and hospital care and a lack of culturally safe health services for the management of HF. The Committee noted that there is limited evidence on the experience of Māori in the setting of HFpEF/HFmrEF specifically but noted that there is evidence of access-related inequities to health services and medicines for Māori in cardiovascular health generally.

Background

8.6. The Committee noted that a funding application for the funding of empagliflozin for heart failure with reduced ejection fraction (HFrEF) was reviewed by PTAC in February 2022 and was recommended for decline due to the limited evidence that empagliflozin offered a health benefit to individuals with HFrEF over currently available treatments.

8.7. The Committee noted that the funding application for empagliflozin in HFrEF was subsequently reviewed by the Cardiovascular Advisory Committee in May 2022 and was recommended for funding with a high priority. The Cardiovascular Advisory Committee considered the high health need and severe impact of HFrEF on the individual and their family/whānau, the evidence showed that empagliflozin provides a health benefit in reducing hospitalisation, reducing all-cause mortality, and improving quality of life in those with HFrEF and the suitability benefit of empagliflozin allowing for the improved adherence with heart-failure treatments.

Health need

8.8. The Committee noted that HF is a complex clinical syndrome with symptoms resulting from abnormalities in cardiac function or structural abnormalities that impair the heart's ability to fill with blood at normal pressure or eject sufficient volumes of blood to fulfil the needs of the body.

8.9. The Committee noted that HFpEF is characterised by abnormal diastolic function, a normal LVEF and normal LV end-diastolic volume. The Committee noted that in HFpEF, the dominant functional abnormality resides in diastole, but there may also be

abnormalities in systolic function, the left atrium, pulmonary vasculature, right ventricle, arteries, and skeletal muscle.

8.10. The Committee noted that HFmrEF shares features of HFpEF but is characterised by some reduction in systolic function, more than seen in HFpEF, usually with progressive chamber dilation and eccentric remodelling.

8.11. The Committee noted that HFpEF/HFmrEF is more difficult to diagnose than HFrEF because the key objective marker of cardiac abnormality (the LVEF) is by definition preserved or mildly reduced. The Committee noted that the clinical symptoms of HFpEF/HFmrEF may be non-specific and the identification of HFpEF/HFmrEF may be dependent on individual propensity to recognise and report symptoms.

8.12. The Committee noted that the management of HFpEF/HFmrEF focuses on providing symptom relief and the management of co-morbidities including hypertension, hyperlipidaemia, atrial fibrillation, and coronary artery disease. The Committee noted that the range of treatments funded for heart failure included ACE-inhibitors, angiotensin-converting enzyme inhibitors; angiotensin receptor blockers; angiotensin receptor-neprilysin inhibitors, mineralocorticoid receptor antagonists.

8.13. The Committee noted that HF was associated with an elevated risk of mortality. The Committee noted that the NHFA CSANZ Heart Failure Guidelines 2018 which reported a 3-year adjusted mortality rate was 32% for HFrEF and 25% for HFpEF. The Committee noted that, unlike HFrEF where a very high proportion of deaths were cardiovascular-related, as much as 30–40% of deaths among individuals with HFpEF were non-cardiovascular.

8.14. The Committee noted that the pathophysiology of HFpEF/HFmrEF is not well-understood, and in part, this contributes to the lack of treatments reported to be effective in reducing the morbidity and mortality associated with HFpEF. The Committee considered there is an unmet health need for individuals with HFpEF/HFmrEF arising from the lack of effective treatments.

8.15. The Committee noted its previous consideration of the health need of family and whānau associated with HFrEF and considered the health need of family and whānau associated with HFpEF/HFmrEF to be as severe as the individual with HFrEF.

8.16. The Committee noted that heart failure falls under one of Pharmac's Hauora Arotahi (Māori health areas of focus): *Manawa Ora - Heart health, high blood pressure and stroke*. The Committee noted that Māori are on average 10 to 15 years younger at age of diagnosis with heart failure, compared to non-Māori. The Committee also noted that Māori with heart failure have higher hospitalisation rates (4 times as likely as non-Māori) and experience reduced survival compared to non-Māori.

8.17. The Committee noted that Māori with HF experience lower access to optimal care compared to non-Māori due to barriers to specialist and hospital care and a lack of culturally safe health services for the management of HF. The Committee noted that there is limited evidence on the experience of Māori in the setting of HFpEF/HFmrEF specifically but noted that there is evidence of access-related inequities to health services and medicines for Māori in cardiovascular health more generally.

8.18. The Committee noted that Pacific people are over twice as likely to be hospitalised for HF compared to non-Māori, non-Pacific people and that Pacific people face barriers and experience treatment gaps when accessing appropriate healthcare to address their cardiovascular needs.

8.19. The Committee considered that funding additional lines of CHF treatments may have the unintended consequence of widening inequities in the management of CHF, especially if access to earlier lines of therapy was inequitable.

8.20. 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

Health benefit

8.21. The Committee noted that empagliflozin reversibly inhibits sodium-glucose co-transporter 2 (SGLT2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion (Jardiance Medsafe Datasheet 2019) and the mechanism at which empagliflozin acts to provide health benefit to individuals with HFpEF/HFmrEF to be uncertain. The Committee noted that Medsafe has approved empagliflozin for adult patients with heart failure (NYHA class II – IV) independent of left ventricular ejection fraction, with or without type 2 diabetes mellitus, to reduce the risk of cardiovascular death and hospitalisation for heart failure and to slow kidney function decline.

8.22. The Committee noted the recent therapeutic recommendations for the treatment of HFpEF/HFmrEF, which graded the evidence to support the use of an SGLT2 inhibitor for the management of HFpEF/HFmrEF to be of moderate strength (American Heart Association/ The American College of Cardiology Foundation/The Heart Failure Society of America (HA/ACC/HFSA) Guideline. Circulation. 2022;145:e895-1032).

8.23. The Committee noted results from the EMPEROR-Preserved trial, a double-blind placebo- controlled trial that reported empagliflozin being associated with a lower risk of its primary composite outcome, which comprised cardiovascular death or hospitalisation for worsening heart failure. The incidence of primary composite events was 6.9 events per 100 patient-years in the empagliflozin group and 8.7 events per 100 patients-years in the placebo group (hazard ratio (HR) 0.79; [95% confidence interval (CI), 0.69 to 0.90]; P<0.001). The trial reported no significant difference in the risk of cardiovascular mortality or all-cause mortality (HR 0.91 [95% CI, 0.76 to 1.09]) and (HR 1.00 [95% CI, 0.87 to 1.15]), respectively) between the empagliflozin and placebo groups (Anker et al. NEJM. 2021;385:1451-61).

8.24. The Committee noted an analysis from EMPEROR-Preserved which reported that empagliflozin treatment was associated with modestly improved Kansas City Cardiomyopathy questionnaire (KCCQ) scores compared to placebo at 52 weeks (mean 1.50 points, [95% CI 0.64 to 2.36]) (Butler et al. Circulation. 2022;145:184-93). The Committee noted that there were several mapping algorithms available to map KCCQ scores to the EQ-5D, a health-related quality of life instrument commonly used for economic assessment.

8.25. The Committee noted a meta-analysis that reported that across 12,251 trial participants in the DELIVER and EMPEROR-Preserved trials, SGLT2 inhibitors reduced composite cardiovascular death or first hospitalisation for heart failure (HR 0·80 [95% CI 0·73–0·87]) with consistent reductions in both components: cardiovascular death (HR 0·88 [95% CI 0·77–1·00]) and first hospitalisation for heart failure (HR 0·74 [95% CI 0·67–0·83]) (Vanduganathan et al. Lancet. 2022;400:757-67).

8.26. The Committee noted the RECEDE-CHF study, where compared with placebo, empagliflozin was associated with a significant increase in 24-hour urinary volume at both day 3 (mean difference, 535 mL [95% CI, 133-936]; P=0.005) and week 6 (mean difference, 545 mL [95% CI ,136-954]; P=0.005) after adjustment for treatment order, baseline 24-hour urine volume, and percentage change in loop diuretic dose. At 6 weeks, empagliflozin was not associated with a significant change in 24-hour urinary sodium

(mean difference, -7.85 mmol/L [95% CI, -2.43 to 6.73]; P=0.57). Empagliflozin was associated with a nonsignificant increase in fractional excretion of sodium at day 3, which was absent at week 6 (mean difference day 3, 0.30% [95% CI ,-0.03 to 0.63]; P=0.09; week 6, 0.11% [95% CI, -0.22 to 0.44]; P>0.99), and a significant increase in electrolyte-free water clearance at week 6 (mean difference, 312 mL [95% CI, 26-598]; P=0.026) compared with placebo (Mordi et al. Circulation. 2020:142:1713-24).

8.27. The Committee noted that empagliflozin reduced HF-related hospitalisations but did not reduce all-cause hospitalisations and considered that HF-related hospitalisations can be associated with ongoing health benefit for the individual in terms of optimisation of a treatment regime.

8.28. The Committee considered that empagliflozin may reduce cardiovascular mortality, however, empagliflozin does not provide benefit to the individual for all-cause related mortality. The Committee also considered that the health-related quality of life (HRQoL) benefit associated with receiving empagliflozin was likely to be modest.

8.29. The Committee considered the opportunity cost of funding empagliflozin when there are other avaliable medicines that may offer greater magnitude of health benefit for individuals with HFpEF/HFmrEF.

8.30. The Committee considered that if empagliflozin were to be funded for treatment of HF it would be ideal to fund it for both reduced ejection fraction and preserved ejection fraction HF, so that the need for an ECHO could be removed from the criteria, which may improve equity of access.

Cost and savings

8.31. The Committee noted estimates from the supplier that there was a population of roughly 35,000 people eligible for empagliflozin, and that between 9,000 to 21,000 individuals may receive empagliflozin if it were to be funded for HFpEF and HFmrEF. The Committee noted that these estimates assumed that uptake among the eligible population would be 30% in the first year of funding and would rise to 60% within four years.

Summary for assessment

8.32. 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 HFpEF and HFmrEF. 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	People with NYHA class II-IV and LVEF >40%.
Intervention	Empagliflozin, 10mg once daily. Taken with optimal standard chronic heart failure treatments.
Comparator(s)	Standard of care
Outcome(s)	Reduced risk of hospitalisation for heart failure • EMPEROR-Preserved reported that empagliflozin treatment was associated with a reduced risk of hospitalisation for heart failure compared to placebo (HR=0.71, 95% CI 0.69 to 0.90) (Anker et al. NEJM. 2021;385: 1451-1461). Improved health-related quality of life • Butler et al. Circulation. 2022;145: 184-193 reported that empagliflozin treatment was associated with improved KCCQ scores compared to placebo at 52 weeks (mean 1.50 points, 95% CI 0.64 to 2.36).
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 target 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.	

9. Silver diamine fluoride - Management of dental caries

Application

9.1. The Committee reviewed a clinician application for silver diamine fluoride (SDF) for the management of mild and moderate tooth caries.

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

Recommendation

9.3. The Advisory Committee **recommended** that silver diamine fluoride (SDF) be listed with a **high** priority.

9.4. In making this recommendation the Committee considered:

9.4.1. The high health need of individuals with mild to moderate dental caries where the current available therapies are not suitable.

9.4.2. The strong evidence demonstrating Māori, Pacific peoples and other populations already experiencing inequitable health outcomes are disproportionately affected by dental caries.

9.4.3. The evidence supporting the cost-effectiveness of SDF in treating dental caries.

9.4.4. The suitability of SDF to be utilised in a variety of non-dental settings and potential to increase the accessibility of dental caries prevention and treatment.

Discussion

Māori impact

9.5. The Committee discussed the impact of funding SDF for the management of dental caries on Māori health areas of focus and Māori health outcomes. The Committee noted that Māori are disproportionately represented in the lowest income brackets, and experience significant barriers to accessing appropriate dental facilities for treatment. Barriers include a lack of culturally appropriate engagement, institutional racism, inequities in opportunities to access education to improve oral health literacy, the geographical setting of clinics and the challenges associated with transportation, work and childcare commitments that need to be navigated to access care. All of these contribute to Māori experiencing differential and inequitable access to the determinants of good oral health (Jamieson & Koopu. J Paediatr Child Health. 2007;43:732-9).

Health need

9.6. The Committee noted that oral health is an integral element of overall health and wellbeing, enabling essential daily function eating, speaking, smiling, and socialising without discomfort pain or embarrassment. Poor oral health significantly impacts an individual's quality of life. The Committee noted the following studies demonstrating the high health need of individuals with dental caries:

- Toi Mata Hauora ASMS. Tooth be told: The case for universal dental care in Aotearoa New Zealand. 2022
- Antunes et al. Pediatr Dent. 2013;35:37-42
- Ky et al. Aust Dent J. 2022; 67:302-13
- Randall et al. Pediatr Dent. 2021;43:223-29
- Antunes et al. Eur Endod J. 2017;3:2-8
- Casamassimo et al. J Am Dent Assoc. 2009;140:650-7.
- Ruff et al. J Am Dent Assoc. 2019;150:111-21
- Robson et al. Oranga Waha. 2011
- Lee et al. Community Dent Oral Epidemiol. 2023;51:388-98
- Shackleton et al. Community Dent Oral Epidemiol. 2018;46:288-96
- Meija et al. BMC Oral Health. 2018;18:176

9.7. The Committee noted that New Zealand's publicly funded dental care is not universal. Children up to the age of 18 years-old can access dental-care without cost. Disabled adults, adults with medical conditions who have been referred to a hospital-based (or associated) dental service by a general or dental practitioner, and individuals with community services cards who require emergency dental care are able to access publicly funded dental care, however there can be associated costs with the care for adults. The Committee considered that as a result of this, the primary group of people who would benefit from funded silver diamine would be children.

9.8. The Committee noted there are several measures for management and prevention of dental caries. In addition to diet modification, fluoride is known to protect the teeth against dental caries and with consistent and thorough brushing with fluoride-containing toothpaste and sufficient fluoride exposure through fluoridation of the water helping limit tooth decay. The Committee noted there are significant inequities in access to such preventive measures, with approximately only 60% of New Zealanders (on a registered water supply) having access to fluoridated water supplies.

9.9. The Committee noted that in the dental setting, application of topical fluoride varnish or fissure sealants can be used as a preventative measure and there are interventions that can address mild to moderate dental caries such as glass ionomer sealants. For more advanced caries, a metal crown can be placed, or the tooth can be drilled to remove the decayed tooth tissue and restored using composite, resin modified glass ionomer or glass ionomer, or ultimately require extraction/removal of the tooth. The Committee noted that invasive dentistry can require time, which is limited in the public system, and in the private system has significant costs associated with it. Operative procedures can also be uncomfortable and/or traumatising experiences that may lead to fear and avoidance of dental treatment for some individuals.

9.10. The Committee considered the health needs for family and whānau of people with dental caries to be unclear due to limited available evidence.

9.11. The Committee noted that there is strong evidence that dental caries disproportionately affect Māori, Pacific peoples and other groups already experiencing health inequities relative to the wider New Zealand population. The Committee noted a recent Pharmac analysis of hospitalisation data for 2019/20 (Te Whatu Ora Publicly Funded Hospitalisations data), which reported 7,117 discharges for dental caries in one year (ICD10 code K02). The data indicated 77% of caries hospitalisations were in children aged 0-9 years (n=5,492) and that the risk of hospitalisations for Māori and Pacific children (0-9 years old) was twice as high as the risk for non-Māori, non-Pacific children (0-9 years old).

9.12. The Committee noted the following publications that address the disproportionate impact and subsequent inequitable oral health outcomes, dental caries can have on Māori, Pacific peoples and other populations already experiencing inequitable health outcomes:

- WAI 2575 Māori health trends 2019 report
- Thornley et al. Int J Paed Dentistry. 2021;31:251-60
- Manatū Hauora New Zealand Health Survey 2021/22
- Whyman et al. Community Dent Oral Epidemiol. 2014;42:234-44
- Lacey et al. NZDJ. 2021;117:105-10
- Peres et al. Lancet. 2019;394:249-60
- Ruiz et al. J. R. Soc. N.Z. 2022;52:265-82
- Jamieson & Koopu. J Paediatr Child Health. 2007;43:732-9
- McKelvey et al. N Z Dent J. 2014;110:58-64
- Public Health Advisory Committee. 2003
- Robson et al. Oranga Waha – Oral Health Research Priorities for Māori: low-income adults, kaumātua, and Māori with disabilities, special needs and chronic health conditions. 2011
- Manatū Hauora, Community Oral Health Service, 2021

9.13. The Committee noted that management of dental caries is not directly related to the government health priorities, however the impact that oral disease has on the individual is significant, and preventing and treating dental caries encompasses the health priorities to improve child wellbeing, mental wellbeing, and health equity.

Health benefit

9.14. The Committee noted that SDF is a clear liquid containing silver, ammonia and 38% (44800ppm) fluoride ions and that one drop of the preparation contains 11.6mg fluoride and is sufficient to treat six teeth with caries. The Committee noted that SDF preparations

are currently not approved by Medsafe for use in New Zealand and noted correspondence from Medsafe that preparations containing fluoride concentrations greater than 5.5mg/ml will need to be registered as a prescription medicine.

9.15. The Committee noted that SDF is applied topically to the tooth. It disrupts the bacterial biofilm, remineralises the previously demineralised inorganic tooth, promotes tooth desensitisation and prevents dentine degradation. The Committee noted that SDF would be used in the management of early and moderate carious lesions.

9.16. The Committee noted the following studies to determine the health benefit SDF provides in the management of dental caries and noted the strength of the evidence differed between different age groups. The Committee considered that the evidence for children and elderly adults was of moderate strength but that the evidence for adults was weak.

- Jain et al. Int J Clin Pediatr Dent. 2023;16:1-8
- Chibinski et al. Caries Res. 2017;51:527-41
- Yawary and Hegde, Int. Dent. J. 2022;72:322-30
- Aly et al. J Dent. 2023;128:104379
- Ballikaya et al. Clin Oral Investig; 2022;26:2197-205
- Ericson et al. Gerodontology. 2022;epub
- Hendre et al. Gerodontology. 2017;34:411-19
- Ruff et al. PLoS One. 2022;17:30261627
- Vollu et al. J Dent. 2019;88:103165

9.17. The Committee considered that funding of SDF would produce a health benefit to family, whānau and wider society, if the individual receiving treatment was able to access SDF application.

9.18. The Committee noted that there is a shortage of dentists, dental specialists and limited dental resources, funding, and access to treatment when general anaesthesia is required. The Committee considered that the simplicity of SDF application to dental caries could limit the need for complex and specialised equipment as it could be applied in an oral health care service, primary care facility or community setting by non-dental community health care workers. The Committee noted there would need to be training and support provided by the health care system to ensure SDF could be utilised in the community.

9.19. The Committee noted that it was unclear how SDF would be implemented into current dental practices and considered that SDF could replace some current dental treatments. The Committee considered that SDF could primarily be utilised as either preventative, bridging or definitive treatment, and that it was not clear from the application or the evidence available which of these uses was likely to be more common.

9.20. The Committee considered that if SDF was used as preventative treatment, then this would not necessarily need to be administered by dentists but could also be done by nurses or hygienists. The Committee considered use of SDF as a preventative treatment would likely result in greater uptake among populations that experience difficulties accessing dental care, as this would not necessarily require that people travel to a dental clinic, in contrast to preventative measures such as fissure sealants. The Committee considered that the target population and the requested use should be clarified, to further understand its likely use.

9.21. The Committee considered that the evidence suggested that outcomes were better when dentists administered SDF, than when dental hygienists were responsible for

administration. The Committee considered that the evidence did however suggest that outcomes were superior for dental hygienist administration of SDF, compared to placebo.

Suitability

9.22. The Committee noted that in paediatric and special care dentistry, there is often a need to slow or stop lesion progression and 'buy time', allowing individuals to develop cognitively and/or acclimatise to community-based dental treating facilities and become more able to cope with restorative treatment solutions performed without the need for sedation or anaesthesia. The Committee noted that SDF treatment can also allow time to engage parents/carers in preventive oral health education and behavioural change (particularly in relation to diet and oral hygiene), to help stop the disease progression.

9.23. The Committee noted that the applicant reports that SDF can be applied in a non-dental setting, which the applicant reports may reduce stress and anxiety for the individual and their whānau or others who are supporting the individual. The wider potential settings for administration also benefited individuals who are unable to access a dental clinic, such as individuals who live rurally or for those who experience difficulties with physical mobility. The Committee considered that this may also help reduce other barriers to accessing community clinics for people without transport, or for those who may also need to navigate other factors (such as work, school, or childcare considerations) to attend this treatment setting.

9.24. The Committee noted that treatment of caries with SDF results in a visible dark stain and this may have cosmetic-related concerns for some individuals and their whānau. The Committee noted that the staining can be partially mitigated by immediately applying potassium iodide after applying SDF. The Committee noted that it was unclear whether an additional potassium iodide step could be used in the non-dental setting, and that may lead to some populations who experience less access to dental infrastructure experiencing greater degrees of tooth staining.

Cost and savings

9.25. The Committee considered that the evidence provided suggests that the staining associated with SDF is not associated with diminished health-related quality of life in children, but the Committee discussed the possibility that teeth staining may be associated with a potential risk of bullying and marginalisation of the children who receive treatment.

9.26. The Committee considered that, based on some news reports on dental treatment in The Waikato, approximately 10% of children would have carious teeth capped. The Committee therefore considered that for a subset of individuals, the comparator would be dental capping.

Summary for assessment

9.27. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for silver diamine if it were funded for the treatment of dental caries. The Committee considered that there were a number of potential ways that silver diamine could be used in New Zealand, and that the most likely PICO would depend on whether there were changes made elsewhere in the health system to facilitate access to SDF. 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 Advisory 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	People receiving publicly funded dental treatment; principally assumed to be children.
Intervention	As preventative treatment: silver diamine fluoride as part of 6-monthly preventative treatment As definitive treatment: silver diamine fluoride as part of SMART. Usage of SDF solution per-treatment is uncertain, UCSF protocol suggests 1 drop may treat up to 5 teeth. The breakdown of definitive and preventative treatment is uncertain, although this is likely to be dependent on whether access to silver diamine fluoride is facilitated such that treatment to a dental clinic is not necessarily required.
Comparator(s)	As preventative treatment: standard dental hygiene visits. As definitive treatment: dental excavation and glass ionomer. - Dental capping may also be a comparator for a proportion of individuals (up to 10%).
Outcome(s)	As preventative treatment: - Improvement in decayed, exfoliated, filled surfaces (DEFS) and reduction in new carious lesions (Jain et al. Int J Clin Pediatr Dent 2023;16:1-8). - Reduction in need for extraction long-term. As definitive treatment: - No difference in arrested lesions, proportion of arrested caries, or proportion of children who are caries-free (Vollu et al. J Dent 2019;88:103165; Aly et al. J Dent 2023;128:104379; Ruff et al. JAMA Netw Open 2023;6:e2255458). Reduction in treatment time of approximately 7 mins (Vollu et al. 2019; Aly et al. 2023).
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 target 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. Octreotide LAR - symptomatic relief in polycystic liver disease

Application

10.1. The Committee reviewed the clinician application for octreotide depot for the treatment of polycystic liver disease.

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

Recommendation

10.3. The Committee **recommended** that octreotide for the treatment of polycystic liver disease be **declined**.

10.4. In making this recommendation the Committee considered that there was a lack of clear health benefit for octreotide, as well as a lack of long-term efficacy data. The Committee considered that clinical trials included a small number of participants and confined their

reporting of outcomes to changes in liver volume, which the Committee considered may not be clinically meaningful.

Discussion

Māori impact

10.5. The Committee noted that polycystic liver disease did not disproportionally affect Māori, however, as Māori are less likely to be referred to specialist services and receive lower than expected levels of quality hospital care than non-Māori (Ellison-Loschmann & Pearce, Am J Public Health. 2006;96:612–7), polycystic liver disease in Māori may be under-diagnosed.

Background

10.6. The Committee noted that octreotide had previously been considered for other indications. The Committee noted that no pharmaceuticals had been previously considered for polycystic liver disease.

Health need

10.7. The Committee noted that polycystic liver disease is a genetic disorder characterised by the progressive development of cholangiocyte-derived fluid-filled hepatic cysts (Masyuk et al. Annu Rev Pathol. 2022; 17:251-69). Polycystic liver disease can present independently, or as an accompanying symptom as a result of autosomal dominant or recessive polycystic kidney disease (Zhang et al. World J Hepatol. 2020; 12:72–83).

10.8. The Committee noted that autosomal-dominant mediated form of polycystic liver disease has, at present, been linked with 12 genes (Masyuk et al. 2022 & Suwabe et al. JHEP Rep. 2020;2:100166).

10.9. The Committee noted that there is no singular diagnostic scale to identify polycystic liver disease, however diagnosis is usually made when the number of hepatic cysts is greater than ten, or alternatively if the individual has a familial history of the condition, is over the age of 40, and is presenting with at least four hepatic cysts.

10.10. The Committee noted that disease severity is commonly measured using the Gigot or Schnelldorfer classification, and classified as mild, moderate, or severe. The majority of individuals presenting with symptomatic polycystic liver disease (up to 94%) are women (Masyuk et al. 2022).

10.11. The Committee noted that polycystic liver disease has been reported to affect approximately 1 in 100,000 individuals (Lewis et al. Clin Liver Dis. 2021;17:238-243). However, the true prevalence is likely to be greater than this, as individuals can also be asymptomatic (Qian et al. Adv Chronic Kidney Dis. 2010; 17: 181–189). The Committee noted that there was no published New Zealand specific epidemiology data but considered there were approximately 33 people in New Zealand living with polycystic liver disease.

10.12. The Committee noted the average age of individuals experiencing symptoms of polycystic liver disease is around 50 years of age (Polycystic liver disease, NORD, 2018).

10.13. The Committee noted that while the volume of the liver in those with polycystic liver disease may increase by 1.8% every 6-12 months, many individuals have minimal or no symptoms (Zhang et al. 2020). The Committee noted that liver volumes are typically 1 litre at baseline, whilst liver volumes of those with symptomatic polycystic liver disease are 3000-5000 ml but can be up to 10,000 ml.

10.14. The Committee noted that approximately 20% of people with polycystic liver disease develop obvious clinical symptoms including dyspnoea, early satiety, abdominal distension, malnutrition, gastroesophageal reflux, back pain due to hepatomegaly pressing on surrounding organs, or cyst complications (Zhang et al. 2020). People with a large number of cysts, or with large cysts, can experience pain from capsular stretch of the liver or pressure symptoms from hepatomegaly (Zhang et al. 2020).

10.15. The Committee noted that in rare cases individuals with polycystic liver disease may develop hepatic venous outflow obstruction due to the cystic mass effect, resulting in portal hypertension, ascites, variceal haemorrhage or splenomegaly (Zhang et al. 2020).

10.16. The Committee noted that those with intrahepatic cysts can experience bleeding, recurrent infection, and hepatic rupture (Crnossen et al. Orphanet J Rare Dis. 2014;9:69).

10.17. The Committee noted that in late-stage disease, liver failure can occur in those with extremely increased liver volumes. Many people with liver failure from severe polycystic liver disease do not meet the Model for End-Stage Liver Disease (MELD) criteria for liver failure, and therefore MELD exception criteria (including assessment of malnutrition and quality of life) should be used instead (Crnossen et al. 2014).

10.18. The Committee noted that in addition to physical symptoms, people with untreated and symptomatic polycystic liver disease score significantly worse on health-related quality of life (HRQoL) measures (Duijzer et al. J Clin Gastroenterol, 2022, 56:731-9).

10.19. The Committee noted that information reported from international general population studies reported that whilst similar numbers of each gender are affected, more women present with severe symptomatic disease than men (Polycystic liver disease. NORD. 2018). This is thought to be due to oestrogen contributing to the growth of liver cysts. Oral contraceptives and oestrogen replacement therapy have also been associated with more severe disease (Polycystic liver disease. NORD. 2018). The Committee noted that liver volume typically increases during the reproductive years and stabilises post-menopause.

10.20. The Committee noted that the initial diagnosis usually occurs with abdominal ultrasound, but further evaluation with computed tomography (CT) or magnetic resonance (MRI) imaging is required.

10.21. The Committee noted that specific polycystic liver disease questionnaires are routinely used by clinicians, as generic measures such as Short Form -36 (SF-36) or EuroQol-5D (EQ-5D) questionnaires have been suggested to not reflect symptomatic burden and loss of quality of life.

10.22. The Committee noted that for those without symptoms, conservative management of the condition is advised with watchful waiting (Masyuk et al, 2022). The primary outcome measurement of polycystic liver disease treatment in symptomatic individuals is liver volume, as well as focusing on the individual's quality of life (Crnossen et al, 2014).

10.23. The Committee noted treatment of those with symptomatic polycystic liver disease is dependent on the type of cysts that are present. The Committee noted aspiration sclerotherapy can be utilised for dominant cysts, whilst fenestration is the most common treatment. The Committee noted that this is usually through laparoscopic surgery and can be repeated if necessary.

10.24. The Committee noted that for areas of minimally affected parenchyma, hepatic resection is considered, however this is not commonly undertaken in New Zealand.

10.25. The Committee noted liver transplantation is the only treatment option for those where hepatic resection is unsuccessful, or in those where there are no areas of preserved

parenchyma. The Committee noted approximately 7 people with polycystic liver disease have received liver transplants in New Zealand over the last 25 years

Health benefit

10.26. The Committee noted Octreotide is a synthetic octapeptide derivative of naturally occurring somatostatin with similar pharmacological effects, but with a considerably prolonged duration of action. It inhibits pathologically increased secretion of growth hormone (GH) and of peptides and serotonin produced within the gastro-entero-pancreatic (GEP) endocrine system.

10.27. The Committee noted that octreotide is not approved by Medsafe for this indication.

10.28. The Committee noted octreotide's dosing is up to 40mg per month via intramuscular injection.

10.29. The Committee noted the Hogan et al, J Am Soc Nephrol, 2010; 21:1052-61 study, a single centre, randomised, double-blind, placebo-controlled trial in 42 people of which 8 had autosomal dominant polycystic liver disease. The study reported that one year after treatment initiation, liver volumes in the octreotide group were 5908 ± 2915 ml and 5557 ± 2659 ml at baseline and 12 months, respectively. Liver volumes in the placebo group were 5374 ± 3565 ml and 5361 ± 3331 ml at the baseline and 12-month visits, respectively. 21/28 in the octreotide group experienced a reduction in liver volume during the 12 months of treatment, which was unaffected by the underlying genotype. On average, liver volume decreased by 4.95% ± 6.77% in the octreotide group compared with a small increase (0.92% ± 8.33%) in the placebo group (P = 0.048, rank-sum test). Absolute changes in liver volume in response to octreotide treatment were significantly correlated with baseline liver volumes, those with larger livers had larger reductions. Two subdomains in the HRQoL questionnaire: physical role, which assesses physical activity (60 to 74, P = 0.04) and bodily pain (68 to 76, P < 0.02 significantly improved in the octreotide-treated group. No significant changes were seen in the placebo-treated group. No other HRQoL subdomains changed significantly over the course of the study.

10.30. The Committee noted the Hogan et al Nephrol Dial Transplant. 2012;27:3532-9 study, which reported the one year open label extension to the Hogan et al. 2010 study to assess safety and clinical benefits of continued use of octreotide LAR for two years, and examined the drug effect in the placebo group who crossed over to octreotide LAR from placebo in year 2. 41/ 42 people received octreotide LAR (n = 28) or placebo (n = 14) in Year 1 and received octreotide in year 2 (maximum dose 40 mg). Placebo showed substantial reduction in total liver volume after treatment with octreotide LAR in year 2 (percentage change (Δ%) -7.66 ± 9.69%, P = 0.011). The initial reduction of total liver volume in the octreotide LAR group was maintained for 2 years (Δ% -5.96 ± 8.90%), although did not change significantly during year 2 (Δ% -0.77 ± 6.82%). Octreotide LAR inhibited renal enlargement during year 1 (Δ% +0.42 ± 7.61%) in the octreotide group and during year 2 (Δ% -0.41 ± 9.45%) in the placebo to octreotide group, but not throughout year 2 (Δ% +6.49 ± 7.08%) in the octreotide group. octreotide LAR -treated individuals continued to experience improvements in QOL in year 2, although overall physical and mental improvements were not significant during year 2 compared to year 1.

10.31. The Committee noted the Hogan et al, Mayo Clin Proc. 2015; 90:1030-7 2 year open label extension to the Hogan et al. 2010 study. Twenty-eight of 42 individuals in a prospective 2-year clinical trial of octreotide LAR (40 mg monthly) consisting of double-blind, randomised (year 1) and open-label treatment (year 2) phases re-enrolled in a 2-year open label extension study after being off treatment for a mean of 8.3 months. Twenty-five (59.5%) completed the open label extension. Off therapy, total liver volume increased by a mean ± SD of 3.4%±8.2% per year; after resuming therapy, total liver volumes decreased by a mean ± SD of -4.7%±6.1% per year. Despite regrowth off treatment, overall reductions were observed, with a median (interquartile range) total liver volume of

4047 mL (3107-7402 mL) at baseline and 3477 (2653-7131 mL) at study completion (-13.2%; P<.001) and with improved health related quality of life.

10.32. The Committee noted the Keimpema et al, Gastroenterology. 2009;137:1661-8.e1-2 study, a randomised, double-blind, placebo-controlled trial in a total of 54 with polycystic liver disease, of which 22 were diagnosed with polycystic liver disease, with 12 treated with lanreotide, a somatostatin analogue, and 7 on placebo, and the remaining people had polycystic kidney disease. Results were reported by treatment arm, and not by underlying disease. The mean liver volume decreased from 4606 (95% CI: 547– 8665) to 4471 (95% CI: 542– 8401) mL in those assigned to 6-month treatment with lanreotide, an average reduction of 2.9% (95% CI: -11.1%–5.4%). 85% showed a decreased. Placebo group had an increase in mean liver volume from 4689 (95% CI: 613– 8765) to 4896 (95% CI: 739 –9053) mL, an average increase of 1.6% (95% CI: -5.2– 8.4%). 27% showed a decrease. No significant changes in gastrointestinal symptoms. The most common adverse effect consisted of loose, pale, and fatty stools (19 patients), which typically started 24 hours after first injection of lanreotide and lasted for 1– 4 days.

10.33. The Committee noted the Pisani et al Clin Gastroenterol Hepatol. 2016;14:1022-1030.e4: single centre controlled study of adults with polycystic kidney and liver disease. Twenty-seven people were randomly assigned to groups given octreotide LAR (40 mg, n = 14) or placebo (n = 13) each month for 3 years. After 3 years, total liver volume decreased by 130.2 ± 133.2 mL in those given octreotide LAR (7.8% ± 7.4%) (P = .003) but increased by 144.3 ± 316.8 mL (6.1% ± 14.1%) in those given placebo. Change vs baseline differed significantly between groups (P = .004). Two years after treatment ended, total liver volume had decreased 14.4 ± 138.4 mL (0.8% ± 9.7%) from baseline in people given octreotide LAR but increased by 224.4 ± 331.7 mL (11.0% ± 14.4%) in individuals given placebo. Changes vs baseline still differed significantly between groups (P = .046). Decreases in total liver volume were similar in each sex; the change in total liver volume was greatest among subjects with larger baseline total liver volume.

10.34. The Committee noted that the numbers included in the trials were very small.

10.35. The Committee noted the end point of liver volume in the studies was a measure of both cyst and parenchymal volume, and therefore reduction of cyst size could not be accurately measured through this endpoint.

10.36. The Committee noted the studies reported results from a combined group of those with polycystic kidney disease with liver cysts and those with polycystic liver disease. The Committee noted there was it was hard to distinguish the effect on those with polycystic liver disease alone.

10.37. The Committee noted the lack of long-term data, with reported results limited to those reported in the Hogan et al. 2015 open label extension study.

10.38. The Committee noted the reduction in liver volumes reached in the first year of treatment were maintained whilst treatment continued. The Committee noted that when treatment was stopped, liver volumes increased.

10.39. The Committee noted the Suwabe et al, PLoS One. 2021; 16: e0257606 metanalysis of seven randomised controlled trials evaluating somatostatin analogue as therapy for those with polycystic kidney disease (PKD) or polycystic liver disease compared to placebo or standard therapy (n=652). The analysis reported that somatostatin analogues are associated with a lower percentage total liver volume growth rate compared to control (mean difference, -6.37%; 95% CI -7.90 to -4.84, p<0.00001).

10.40. The Committee noted the Neijenhuis et al Aliment Pharmacol Ther. 2015;42:591-8 pooled analysis from two randomised double-blind, placebo-controlled trials that evaluated health-related quality of life using the SF-36 in 96 individuals with polycystic liver disease

treated for 6-12 months with somatostatin analogues or placebo. Physical component scores improved with somatostatin analogues but remained unchanged with placebo (3.41 ± 1.29 vs. -0.71 ± 1.54, P = 0.044). Treatment had no impact on the mental component score. Large liver volume was independently associated with larger HRQoL decline during follow up (-4.04 ± 2.02 points per logarithm liver volume, P = 0.049).

10.41. The Committee noted the Gevers et al Gastroenterology. 2013;145:357-65.e1-2 meta-analysis pooling three randomised placebo-controlled trials (n=107) in people with polycystic liver disease or polycystic kidney disease treated with somatostatin analogues. The study reported that the effects of somatostatin therapy did not differ significantly among those with different diagnoses or baseline liver volumes; the overall difference in liver volume between groups receiving somatostatin analogues therapy vs placebo was 5.3% (P < .001). Among those given placebo, younger women (≤48 years old) had the greatest increase in polycystic liver volume (4.8%; 95% confidence interval: 2.2%-7.4%), and mean liver volumes did not increase in older women and men. Women ≤48 years old had a greater response to therapy (a reduction in liver volume of 8.0% compared with placebo; P < .001) than women ≥48 years (a reduction in liver volume of 4.1% compared with placebo; P = 0.022).

10.42. The Committee noted the Caroli et al, Clin J Am Soc Nephrol. 2010;5:783-9 post hoc analysis of a prospective, randomised, crossover, double-blind, placebo-controlled study that reported that 6 months of octreotide therapy limited kidney volume growth versus placebo in 12 people with polycystic kidney disease. Liver volumes significantly decreased from 1595 ± 478 ml to 1524 ± 453 ml with octreotide, whereas they did not appreciably change with placebo. Changes in liver volumes were significantly different between the two treatment periods (−71 ± 57 ml versus +14 ± 85 ml). Octreotide-induced liver volume reduction was fully explained by a reduction in parenchyma volume from 1506 ± 431 ml to 1432 ± 403 ml. Changes in liver volumes were significantly correlated with concomitant changes in kidney volumes (r = 0.67) during octreotide but not during placebo treatment. Liver and kidney volume changes significantly differed with both treatments (octreotide: −71 ± 57 ml versus +71 ± 107; placebo: +14 ± 85 ml versus +162 ± 114), but net reductions in liver (−85 ± 103 ml) and kidney (−91 ± 125 ml) volume growth on octreotide versus placebo were similar.

10.43. The Committee noted that liver volume reduction reported in Caroli et al. 2010 study was mainly due to a reduction in the liver parenchyma.

10.44. The Committee noted Hogan et al. 2010 study reported 61% had grade 1 diarrhoea, abdominal cramping, bloating, and gas was reported in 50% of individuals compared to 28 and 21% respectively in the placebo arm.

10.45. The Committee noted the Griffiths et al. BMJ Open. 2020; 10: e032620 metanalysis that reported the relative risks adverse events of somatostatin analogue treatment pooling five studies in a total of 500 people. The analysis reported that somatostatin analogue treatment increased the risk of side effects including diarrhoea (relative risk [RR] 4.83), abdominal pain (RR 2.86), cholelithiasis and cholecystitis (RR 4.8), alopecia (RR 5.88), and discontinuation risk (RR 2.64).

10.46. The Committee considered there was similar efficacy of octreotide to other somatostatin analogues including lanreotide.

Suitability

10.47. The Committee noted that octreotide could be administered in a primary health care setting.

10.48. The Committee noted that octreotide is formulated as two separate vials of a powder and diluent that need to be reconstituted.

Cost and savings

10.49. The Committee considered that polycystic liver disease is a relatively unique condition, and as a result, there are no analogous conditions from which to infer health-related-quality-of-life outcomes.

10.50. The Committee noted that current treatment of polycystic liver disease consists of the following: observation, aspiration (of dominant cyst(s)), fenestration (most common technique according to surgeons), hepatic resection (not common) and liver transplant. The Committee considered that less than 1% of those receiving liver transplants have polycystic liver disease, and so liver transplantation is rare in this setting. The Committee therefore considered that it was unlikely that funding octreotide would be associated with a change in the number of liver transplants.

10.51. The Committee noted the comparator in the PICO is not appropriate, individuals will visit their surgeon and receive the most appropriate/effective surgery such as fenestration, which could be repeated as required to derive symptomatic benefit. Hence, repeat surgical procedures are standard.

10.52. The Committee considered there was no evidence to suggest octreotide would result in any significant changes to health sector expenditure. The Committee considered that there was no strong evidence of an association between a reduction in liver volume in this setting, and a reduction in health resource utilisation. The Committee considered that there was insufficient evidence to suggest that octreotide treatment would be associated with a reduction in the number of surgical procedures required.

10.53. The Committee considered that there was no data linking octreotide treatment with lower mortality in this setting. The Committee considered that while there is evidence linking liver volume and mortality, it could not be inferred that a reduction in liver volume from octreotide in this setting would be associated with lower mortality. The Committee considered that the evidence linking liver volume to mortality is based in other disease areas and the relationship was likely to be confounded by other factors, including comorbidity.

10.54. The Committee considered that in terms of benefits or outcomes of octreotide use, symptom relief would be the most appropriate to consider. The Committee considered that based on the SF-6D improvements, there was likely to be a health-related quality of life improvement, though this is likely to be relatively low.

10.55. The committee considered that consultation with surgeons in Auckland reported around three to four laparoscopic fenestrations a year. The applicant said he had two individuals under his care with polycystic liver disease, so generalising to the New Zealand population there might be 15 individuals wanting surgery, who might consider octreotide instead.

10.56. The Committee considered that octreotide may delay time to liver resection, fenestration, or transplantation by one to two years. However, the Committee considered that this was a speculative assumption and there was no data available to confirm this.

Summary for assessment

10.57. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for octreotide for the treatment of symptomatic polycystic liver disease. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory 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	Individuals with severe, symptomatic polycystic liver disease.
Intervention	Octreotide at 40mg, monthly by SC injection - Discontinuation of octreotide led to liver volume increases, so treatment considered to be ongoing.
Comparator(s)	Best supportive care, which would include repeat surgical procedures (aspiration sclerotherapy, fenestration, hepatic resection)
Outcome(s)	**Intermediate endpoint** Liver volume - Octreotide reduced liver volume compared to placebo (Hogan et al, 2012) **Hard clinical outcomes** All-cause mortality - Insufficient evidence to suggest that octreotide is associated with all-cause mortality, or that a reduction in liver volume would be associated with lower mortality. Health-related quality of life (HRQOL) - SF-36 reported physical role, which assesses physical activity (60 to 74, P = 0.04) and bodily pain (68 to 76, P < 0.02 significantly improved in the octreotide-treated group (Hogan et al, 2012). However, the Prescription for Pharmacoeconomic Analysis (PFPA) recommends the use of EQ-5D to measure HRQOL in the context of economic assessment. Transplantations - Insufficient evidence that octreotide would reduce liver transplantation, and number of liver transplants attributable to PLD is small.

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 target 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.

11. Upadacitinib for the first and/or second line biologic treatment of severe ulcerative colitis and Crohn's disease

Application

11.1. The Committee reviewed the supplier application for upadacitinib for the first and/or second line biologic treatment of ulcerative colitis and Crohn's disease.

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

Recommendation

11.3. The Committee **recommended** that upadacitinib be listed for the treatment of ulcerative colitis with a **medium priority** for first line biologic treatment**,** and **high** for second line biologic treatment. The Committee recommended the Special Authority criteria below for the first-line setting:

Initiation –ulcerative colitis
Applications from any relevant practitioner. Approvals valid for 6 months for application meeting the following criteria:
Both:

1. Patient has histologically confirmed ulcerative colitis; and
2. Any of the following:
   2.1. Patient has had an initial approval for prior biologic therapy and has experienced intolerable side effects or insufficient benefit to meet renewal criteria (unless contraindicated) or
   2.2. Patients has a SCCAI core greater than or equal to 4; or
   2.3. Patients PUCAI score is greater than or equal to 20 and
3. Any of the following
   3.1. Patient has tried but had experienced an inadequate response to (including lack of initial response and/or loss of initial response) from prior therapy with immunomodulators and corticosteroids; or
   3.2. Patient has experienced intolerable side effects from immunomodulators and corticosteroids; or
   3.3. Immunomodulators and corticosteroids are contraindicated; and

Renewal –ulcerative colitis
Applications from any relevant practitioner. Approvals valid for 2 years for any application meeting the following criteria:
Both
1. Either:
   1.1. The SCCAI score has reduced by 2 points or more from the SCCAI score when the patient was initiated on biological therapy; or
   1.2. The PUCAI score has reduced by 10 points or more from the PUCAI score since initiation on biological therapy and;
2. Upadacitinib will be used at a dose no greater than 30mg once daily for maintenance therapy.

11.4. In making this recommendation the Committee considered the unmet health need of those with ulcerative colitis, the health benefit of upadacitinib in the treatment of ulcerative colitis and the suitability of the oral formulation of upadacitinib, reducing the need for injections or infusions compared with other funded biologics.

11.5. The Committee **recommended** that upadacitinib for the treatment of Crohn's disease be **deferred** until further evidence and the results of phase 3 trials in this setting are published.

Discussion

Māori impact

11.6. The Committee considered that whilst data suggested that Māori and Pacific peoples were under-represented in the Crohn's disease or ulcerative colitis population, it is possible that equity issues including access to healthcare specialists may affect diagnosis, and therefore the current data may not accurately reflect the actual incidence and prevalence of inflammatory bowel disease (IBD) in some populations.

11.7. The Committee noted that few individuals receiving biologic treatment for ulcerative colitis were Māori (6%) or Pacific peoples (1%) (as of 30 June 2021; PharmHouse data).

Background

11.8. The Committee noted that it had previously reviewed upadacitinib for other indications. The Committee noted that it had recently reviewed ustekinumab for the first-line treatment of ulcerative colitis and Crohn's disease in February 2023. The Committee recommended widening access to ustekinumab to first line biologic use for those with Crohns disease or ulcerative colitis with a low priority.

11.9. The Committee noted that the Gastrointestinal Advisory Committee reviewed upadacitinib for those with moderate to severe ulcerative colitis in those who have responded inadequately to either infliximab or adalimumab therapy in August 2022, and recommended it for funding with a high priority.

Health need

11.10. The Committee noted it has considered and discussed the high health need of the population during previous considerations of inflammatory bowel disease. The Committee considered the health need has not changed since this consideration in February 2023.

11.11. The Committee noted the funded treatments for ulcerative colitis and Crohn's disease are the same, with recent funding of vedolizumab and ustekinumab allowing vedolizumab at any line of treatment, and ustekinumab as a second-line treatment.

Health benefit

Ulcerative colitis

11.12. The Committee noted the studies reviewed by the Gastrointestinal Committee in August 2022.

11.13. The Committee noted the supplier network metanalysis, that was performed in 2021, indirectly comparing upadacitinib with ustekinumab and vedolizumab across trials.

11.14. The Committee noted the Ma et al, Aliment Pharmacol Ther. 2019;50:5-23 systematic review of 12 random controlled trials (5 Crohns Disease [CD], 7 ulcerative colitis[UC]) were included. People were randomised to placebo (n = 844), or JAK inhibitors: tofacitinib (n = 1882), filgotinib (n = 130), peficitinib (n = 176), upadacitinib (n = 387) or TD-1473 (n = 31). JAK inhibitor treatment was associated with induction of clinical remission in CD (relative risk [RR] 1.38 [95% confidence interval [CI] 1.04-1.83], P = 0.025, I^2 = 14%) and UC (RR 3.07 [95% CI 2.03-4.63], P < 0.001, I^2 = 0%). In UC, JAK inhibitor treatment was associated with induction of endoscopic remission (endoscopic Mayo subscore MCSe = 0/1) (RR 2.43 [95% CI 1.64-3.59], P < 0.001, I^2 = 27%) and mucosal healing (MCSe = 0) (RR 5.50 [95% CI 2.46-12.32], P < 0.001, I^2 = 0%). JAK inhibitor treatment increased the risk of infection compared to placebo (RR 1.40 [95% CI 1.18-1.67], P < 0.001, I^2 = 0%), particularly for herpes zoster.

11.15. The Committee noted the Olivera et al, Gastroenterology. 2020;158:1554-1573.e12. systematic review and meta-analysis that included 82 studies including 66,159 people with immune-mediated diseases (rheumatoid arthritis, inflammatory bowel diseases, psoriasis, or ankylosing spondylitis.) who were exposed to a JAK inhibitor. The incidence rate of adverse events (AEs) was 42.65 per 100 person-years and of serious AEs was 9.88 per 100 person-years. Incidence rates of serious infections, herpes zoster infection, malignancy, and major cardiovascular events were 2.81 per 100 person-years, 2.67 per 100 person-years, 0.89 per 100 person-years, and 0.48 per 100 person-years, respectively. Mortality was not increased in patients treated with JAK inhibitors compared with patients given placebo or active comparator (relative risk 0.72; 95% confidence interval 0.40-1.28). The meta-analysis showed a significant increase in risk of herpes zoster infection among patients who received JAK inhibitors (relative risk 1.57; 95% confidence interval 1.04-2.37).

11.16. The Committee noted the Din et al, Aliment Pharmacol Ther. 2023;57:666-675 network meta-analysis of 25 trials (n=9935). Only tofacitinib 10 mg twice daily (RR = 6.90; 95% CI 1.56-30.63, number needed to harm (NNH) = 97; 95% CI 19-1022) and upadacitinib 45 mg o.d. (RR = 7.89; 95% CI 1.04-59.59, NNH = 83; 95% CI 10-14,305) were significantly more likely to increase risk of Herpes zoster infection. JAK inhibitors were the most likely drug class to increase risk of infection, and risk increased with higher doses (RR with lowest dose = 3.16; 95% CI 1.02-9.84, NNH = 265; 95% CI 65-28,610, RR with higher dose = 5.91; 95% CI 2.21-15.82, NNH = 117; 95% CI 39-473).

11.17. The Committee considered that there may be a use for those with severe ulcerative colitis acutely. The Committee noted that due to low albumin levels, treatment with

infliximab in the acute setting requires a significantly higher dose to achieve therapeutic levels. The Committee noted other treatments did not require a higher dose in this setting and provided a rapid time to remission.

11.18. The Committee noted it could also be of benefit to those who may potentially require hospital admission to provide remission in a non-hospital setting.

Crohn's disease

11.19. The Committee noted the Sandborn et al, Gastroenterology 2020;158:2123–2138 double-blind, phase 2 trial in 220 people with moderate to severe Crohn's disease and inadequate response or intolerance to immunosuppressants or tumour necrosis factor antagonists. Primary endpoints were clinical remission at week 16 and endoscopic remission at week 12 or 16. The study reported that clinical remission was achieved by 13% on 3 mg, 27% on 6 mg (P < 0.1 vs placebo), 11% receiving 12 mg, and 22% of receiving 24 mg twice daily, and 14% receiving 24 mg once daily, vs 11% of placebo. The study reported endoscopic remission was achieved by 10% (P <0.1 vs placebo), 8%, 8% (P <0 .1 vs placebo), 22% (P <0 .01 vs placebo), and 14% (P < 0.05 vs placebo) of those receiving upadacitinib, respectively, vs none of the individual receiving placebo. Endoscopic but not clinical remission increased with dose during the induction period. Efficacy was maintained for most endpoints through week 52. During the induction period upadacitinib groups had higher incidences of infections and serious infections vs placebo. The twice-daily 12 mg and 24 mg upadacitinib groups had significant increases in total, high-density lipoprotein, and low-density lipoprotein cholesterol levels compared to placebo group.

11.20. The Committee noted a clinical study report provided by the supplier for the U-EXCEL (431) study, which was a multicentre, randomised, double-blind, placebo-controlled induction study of the efficacy and safety of upadacitinib in those with moderately to severely active Crohn's disease where the disease had inadequately responded to, or the individual was intolerant to biologic therapy. A statistically significantly greater (p-value < 0.0001) proportion in the upadacitinib 45 mg group achieved the co-primary endpoint of clinical remission (defined by Crohn's Disease Activity Index [CDAI] and PROs) compared to placebo group. At Week 12, a statistically significantly greater (p-value < 0.0001) proportion in the upadacitinib 45 mg group achieved endoscopic response, compared to the placebo. Eight out of 10 key secondary endpoints were achieved. The study reported upadacitinib demonstrated symptom relief across clinical measures (clinical remission, clinical response, steroid-free clinical remission, fatigue), in objective measures of inflammation and quality of life measures. Rapid onset of action was observed by the achievement of clinical response 100 (CR-100) as early as from Week 2 with statistically significant differences observed for upadacitinib 45 mg QD versus placebo, and clinical remission at Week 4. Endoscopic remission and steroid-free clinical remission were also achieved at Week 12, with statistically significant differences observed for upadacitinib 45 mg QD versus placebo. Patient reported outcome (PRO) questionnaires also showed overall statistically significantly higher improvement in upadacitinib 45 mg versus placebo. CD-related hospitalisations were numerically lower in the upadacitinib 45 mg group versus placebo.

11.21. The Committee noted a clinical study report provided by the supplier for the U-EXCEL (433) study that was a phase 3, randomised, double-blind, placebo-controlled induction study in those with moderately to severely active Crohn's Disease who have inadequately responded to or are intolerant to conventional and/or biologic therapies. At Week 12, a statistically significantly greater (p-value < 0.0001) proportion of people in the upadacitinib 45 mg group achieved the co-primary endpoint of clinical remission (defined by CDAI /PROs for the) compared to placebo group. At Week 12, a statistically significantly greater (p-value < 0.0001) proportion of people in the upadacitinib 45 mg group achieved endoscopic response, compared to the placebo group. Eight out of 10 key secondary endpoints were achieved. The study reported upadacitinib demonstrated symptom relief

across clinical measures (clinical remission, clinical response, steroid-free clinical remission, fatigue), in objective measures of inflammation, and quality of life measures. Rapid onset of action was observed by the achievement of CR-100 as early as from Week 2, with statistically significant differences observed for upadacitinib 45 mg QD versus placebo, and clinical remission at Week 4. Endoscopic remission and steroid-free clinical remission were also achieved at Week 12, with statistically significant differences observed for upadacitinib 45 mg QD versus placebo. PRO questionnaires reported an overall statistically significantly higher improvement in upadacitinib 45 mg versus placebo.

11.22. The Committee noted a clinical study report provided by the supplier for the U-ENDURE (430) study that was a multicentre, randomised, double-blind, placebo-controlled maintenance and long-term extension study in those with moderately to severely active Crohn's disease who have achieved clinical response and completed the induction studies 431 or 433. The study reported superiority of upadacitinib 15 mg QD and upadacitinib 30 mg compared to placebo was demonstrated for the co-primary endpoints of clinical remission (per CDAI and PROs) and endoscopic response at Week 52. The efficacy of upadacitinib 15 mg and 30 mg treatment vs placebo as a maintenance therapy was demonstrated based on assessment of disease activity and symptoms, objective measures of inflammation, and quality of life. The study reported the 30 mg dose demonstrated higher efficacy rates than 15 mg across the co-primary and all key secondary endpoints. In patients who had delayed response to the induction therapy (upadacitinib 45 mg non-responders, who responded at Week 24 while on upadacitinib 30 mg), benefit was observed with maintenance therapy of upadacitinib 30 mg, as shown in disease activity and symptoms, endoscopic and markers of inflammation, and quality of life measure.

11.23. The Committee noted the evidence in the clinical study reports provided by the supplier were not peer reviewed and published data. The Committee noted most trials are in comparison to placebo.

11.24. The Committee noted the data was immature, with some trials provided determining the optimal dosing of upadacitinib, rather than phase three studies to determine safety and efficacy in comparison to other biologic treatments.

11.25. The Committee noted that there was weak emerging evidence that may indicate higher rates of infection and lipid dysfunction in those treated with upadacitinib.

11.26. The Committee noted the supplier provided Bayesian network meta-analysis, based on a systematic literature review of 18 random controlled trials, conducted in May 2022. The analysis reported upadacitinib to be the most effective in both biologic-naïve and biologic-experienced individuals. The Committee noted there were some important limitations to the supplier NMA, including differences in patient populations and differences in trial design across trials. The Committee noted that this was not peer reviewed and published data.

11.27. The Committee noted the following studies:

- D'Haens et al, Clin Gastroenterol Hepatol. 2022;20:2337-46.e3.
- Peyrin-Biroulet et al, Adv Ther. 2021;38:2339-52.
- Mohamed et al, Clin Pharmacol Ther. 2020;107:639-49
- Rokkas et al, J Gastrointestin Liver Dis. 2021;30:388-97

11.28. The Committee noted the Barberio et al, Gut. 2023;72:264-74 meta-analysis that compared of 25 induction of remission trials (n=8720). Based on failure to achieve clinical remission the analysis reported infliximab 5 mg/kg ranked first versus placebo (RR=0.67, 95% CI 0.56 to 0.79, p-score 0.95), with risankizumab 600 mg second and upadacitinib 45 mg once daily third. The analysis reported in 15 maintenance of remission trials (4016

patients), based on relapse of disease activity, upadacitinib 30 mg once daily ranked first (RR=0.61, 95% CI 0.52 to 0.72, p-score 0.93).

Suitability

11.29. The Committee noted administration of the treatment by way of an oral tablet eliminates the need for an individual to self-inject an alternative subcutaneous treatment or reduce carer burden where self-administration is not possible. The Committee noted this formulation would also reduce travel time for the person and their family to infusion centres for those biologics that require intravenous infusions.

11.30. The Committee noted this was of particular benefit to those in rural areas, or for those with a reduced access to infusion services.

Cost and savings

11.31. The Committee considered there was no evidence at present to suggest what uptake may be for upadacitinib in ulcerative colitis. The Committee considered that uptake would likely be high, given the patient and clinician desire for suitable treatments. The Committee considered that adalimumab had comparatively low response and remission rates in UC, and that upadacitinib would be a favourable alternative in the first-line setting. The Committee considered that the suitability of upadacitinib would also likely drive high second-line uptake.

11.32. The Committee considered that upadacitinib uptake in the first line setting for Crohn's may be lower than in ulcerative colitis due to the efficacy of subcutaneous adalimumab in this setting, but that uptake in the second line setting for Crohn's disease would likely be high, noting the favourable suitability and the lack of a need for IV treatment for either induction or maintenance.

11.33. The Committee considered that the UC data suggested response and remission rates were higher for the 30mg dose, compared to the 15mg dose, and considered this would likely be similar for Crohn's disease. The Committee considered that in UC, people may receive the higher dose 70-80% of the time. The Committee considered that people who experience treatment success on the higher dose would be unlikely to drop to a lower dose. The Committee considered that the proportion of people receiving the higher dose for Crohn's disease would not be lower than for UC, and would potentially be higher, given the greater disease severity.

Summary for assessment

11.34. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for upadacitinib were funded to allow use as a first or second-line biologic treatment for ulcerative colitis. 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 develop based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Individuals with moderate-severe UC who have experienced inadequate benefit from prior conventional and/or biologic therapy Individuals may receive upadacitinib as a first-line treatment, or may receive upadacitinib after failure of a biologic agent
Intervention	Upadacitinib, 45mg once-daily for first 12 weeks, followed by 15mg or 30mg daily thereafter - Proportion of people receiving each of 15mg and 30mg dosage for maintenance is uncertain, likely to be 70-80%
Comparator(s) (NZ context)	Funded biologic therapy. First-line, comparator estimated to be: - Adalimumab (~35%) - Infliximab (~35%) - Vedolizumab (~30%)
Outcome(s)	Improved rates of clinical response and remission compared to supportive care. - Improved rates of clinical response and remission assumed to be associated with lower health system costs associated with poorly controlled UC. Uncertain magnitude of benefit compared to funded biologic treatments, in either a first- or second line setting. - Trend towards benefit vs other agents, however differences in patient populations and trial designs impair comparisons.

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 target 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.