PHARMAC
TE PĀTAKA WHAIORANGA

Pharmacology and Therapeutics Advisory Committee
Objective advice to Pharmac

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# Record of the Pharmacology and Therapeutics Advisory Committee Meeting

## Held on 14 February 2025

**This meeting was held in person and via Microsoft Teams**

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## 1. Present

**PTAC members:**
Stephen Munn (Temporary Chair, on behalf of the Acting Chair)
Brian Anderson
Bruce King
Elizabeth Dennett
Helen Evans
James Le Fevre
John Mottershead
Liza Lack
Matthew Dawes
Matthew Strother
Robyn Manuel

**Apologies:**
Rhiannon Braund (Acting Chair)
Paul Vroegop

## 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

| | Pharmaceutical and Indication | Recommendation |
|---|---|---|
| 8.3 | Ferric derisomaltose to prevent iron deficiency (with or without anaemia) in people with hereditary haemorrhagic telangiectasia, subject to Special Authority criteria | High Priority |
| 9.3 | Rituximab for the maintenance treatment of antineutrophilic cytoplasmic antibody (ANCA) associated vasculitis be listed with no restriction on treatment duration, subject to amended Special Authority criteria | High Priority |
| 10.3 | Nivolumab with ipilimumab for the treatment of malignant pleural mesothelioma of the sarcomatoid or biphasic subtypes, subject to Special Authority criteria | Medium Priority |
| 10.4 | Nivolumab with ipilimumab for the treatment of malignant pleural mesothelioma (any subtype), subject to Special Authority criteria | Low Priority |
| 11.4 | Liraglutide in the weight management of either (1) individuals with a body mass index (BMI) 55kg/$m^2$and over, with high cardiovascular risk, without type two diabetes mellitus (T2DM), unable to access publicly-funded bariatric surgery; or (2) Māori and/or Pacific people with BMI 50kg/$m^2$and over, with high cardiovascular risk, without T2DM, subject to Special Authority criteria | Low Priority |
| 12.3 | Widening access to benralizumab for the first-line treatment of eosinophilic granulomatosis with polyangiitis (EGPA), subject to Special Authority criteria | High Priority |
| 12.4 | Widening access to benralizumab and mepolizumab for the second-line treatment of eosinophilic granulomatosis with polyangiitis (EGPA), subject to Special Authority criteria | Medium Priority |

## 4. Record of PTAC meeting held 14 November & 15 November 2024

4.1. The Committee did not review the record of the PTAC meeting held on 14 November & 15 November 2024 as this was not yet ready.

## 5. Action Points

5.1. There were no current action points.

## 6. Pharmac Update

6.1. The Committee noted the Pharmac Update.

6.2. Pharmac staff updated the Committee on a proposed Expert Advice Review, as well as a summary of the Societal Perspectives Pilot underway, the Medical Devices programme, and PTAC recruitment.

6.3. The Committee discussed the Consumer Independent Report, acknowledging the report will be presented to Board in February of 2025 and later shared with the public.

## 7. Specialist Advisory Committee Records

### August 2024 Respiratory Specialist Advisory Committee Record

7.1. PTAC reviewed the records of the Respiratory Advisory Committee meeting held on 28 August 2024.

7.2. PTAC noted the records including the Advisory Committee's recommendations.

### September 2024 Immunisation Specialist Advisory Committee Record

7.3. PTAC reviewed the records of the Immunisation Specialist Advisory Committee held on 5 September 2024.

7.4. PTAC noted the records including the Advisory Committee's recommendations.

### October 2024 Mental Health Specialist Advisory Committee Record

7.5. PTAC reviewed the records of the Mental Health Advisory Committee meeting held on 25 October 2024.

7.6. PTAC noted the records including the Advisory Committee's recommendations.

## 8. Ferric derisomaltose - hereditary haemorrhagic telangiectasia (HHT), to prevent iron deficiency/anaemia

### Application

8.1. The Committee reviewed the clinician and consumer applications for the use of ferric derisomaltose (Monofer) for the prevention of iron deficiency and/or anaemia in people with hereditary haemorrhagic telangiectasia (HHT), and noted the supplementary information received from the supplier for this indication.

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 ferric derisomaltose be funded to prevent iron deficiency (with or without anaemia) in people with hereditary haemorrhagic telangiectasia with a **high priority**, subject to the following Special Authority criteria:

> **FERRIC DERISOMALTOSE**
> **Initial application — hereditary haemorrhagic telangiectasia (HHT)**
> Applications from any relevant practitioner. Approvals valid without further renewal unless notified.
> Both:
> 1. Patient has been diagnosed with hereditary haemorrhagic telangiectasia (HHT); and
> 2. Patient experiences recurrent bleeding and is expected to require regular iron infusions; and
> 3. Either:
>  3.1. Serum ferritin is less than or equal to 50 mcg/L; or
>  3.2. Transferrin saturation is less than or equal to 20%.

8.4. In making this recommendation, the Committee considered:

8.4.1. the high health needs of people with HHT who experience chronic, frequent blood loss and recurrent iron deficiency requiring frequent intravenous (IV) iron infusions, where frequent iron infusions place them at a greater risk of experiencing short-term effects from hypophosphatemia such as fatigue

8.4.2. that ferric derisomaltose (FDI) has a favourable adverse effect profile compared with ferric carboxymaltose (FCM), which is especially relevant in the context of frequent iron infusions and the risk of hypophosphatemia

8.4.3. that FDI and FCM have equivalent efficacy in terms of iron repletion

8.4.4. that treatment with FDI at the lower threshold proposed (ie where there is iron deficiency without anaemia) aligns with expert opinion and international treatment guidelines for management of HHT, given that the recurrent blood loss in this condition is expected to result in anaemia.

## Discussion

*Māori impact*

8.5. The Committee discussed the impact of funding FDI for the prevention of iron deficiency and/or anaemia in people with HHT on the Pharmac Māori Health Areas of Focus | Hauora Arotahi and Māori health outcomes. The Committee considered the comments made in PTAC's August 2024 consideration of ferric carboxymaltose (Ferinject, FCM) for people with HHT including Māori remained relevant.

*Populations with high health needs*

8.6. The Committee discussed the health need(s) of people with HHT among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs. The Committee considered the comments made in PTAC's August 2024 consideration of FCM for people with HHT including populations with high health needs remained relevant.

*Background*

8.7. The Committee noted that FCM is currently funded with restrictions for people with anaemia (low haemoglobin) with or without iron deficiency or with certain chronic and/or inflammatory diseases.

8.8. The Committee noted that in August 2024, PTAC considered applications requesting widened access to FCM for people with HHT with a serum ferritin of 50 mcg/L or less or transferrin saturation of 20% or less. At that time, PTAC recommended that the applications be declined, and considered the following:

- the high health need of people with HHT and especially the unmet need due to chronic iron deficiency and challenges with timely access to a suitable iron replacement product
- that the evidence base in HHT is limited, as expected for a relatively rare disease. However, there was insufficient evidence (in this disease and extrapolated from other indications) of significant clinical benefits from changing the threshold to access FCM as proposed
- the increased risk of hypophosphatemia where FCM is used repeatedly and poor awareness of this safety concern among New Zealand clinicians prescribing FCM
- that the hypophosphatemia risk is the reason that international treatment guidelines for HHT do not recommend repeated use of FCM in this disease, and instead recommend other iron products be used where available
- that a different intravenous (IV) iron product may more appropriately address the unmet health need of people with HHT with iron deficiency
- that Pharmac should encourage funding application(s) for other IV iron treatment(s) with better safety profiles and accompanied by evidence of benefit if available, noting that HHT clinical management guidelines list several iron products considered by experts to be suitable for use in the disease

- that Pharmac should consider engaging with health sector partners such as the Goodfellow Unit to increase prescriber awareness of the hypophosphatemia risk and management with repeat infusions of FCM.

*Health need*

8.9. The Committee noted that the high health needs of people with HHT who experience chronic, frequent blood loss and recurrent iron deficiency requiring frequent intravenous (IV) iron infusions were considered by PTAC in August 2024. The Committee noted the key safety concern with FCM is hypophosphatemia and that the following were also discussed at that time in the context of HHT:

8.9.1. the risk of developing alloimmunity from repeated blood cell transfusions

8.9.2. the association (not necessarily causative) between low serum iron and ischaemic stroke in people who had pulmonary arteriovascular malformations (AVMs)

8.9.3. the increased risk of venous thromboembolism (VTE) with low iron or transferrin saturation, which may be mediated by increased factor VIII in response to low iron.

8.10. The Committee considered that there is no standardised algorithm for phosphate monitoring post-iron infusion used in New Zealand. Members considered that hypophosphatemia can occur following a single dose of IV iron and therefore this is not necessarily a cumulative risk. The Committee noted that the risk of hypophosphatemia with iron infusions of FCM or iron polymaltose had been highlighted in a recent prescriber update issued by Medsafe (Medsafe, December 2024). Medsafe reported there were 45 case reports of hypophosphatemia following parenteral iron infusions reported between 2016 and 2024 in New Zealand. Of these 45 reports, 39 were in females, 44 were associated with FCM, and 40 were serious. There were no reports of osteomalacia or fracture with these medicines. Members considered this an underrepresentation of the number of people experiencing hypophosphatemia from IV iron given that most cases would only present symptomatically.

8.11. The Committee considered the following evidence for adverse effects related to hypophosphatemia occurring with IV iron, irrespective of the iron's presentation:

8.11.1. The Committee noted two studies in people receiving IV iron treatment, one in inflammatory bowel disease (IBD) and another in a general population, which both reported fatigue was associated with low serum phosphate (Zoller et al. Gut. 2023;72:644-53; Hardy et al. Int J Rheumatol. 2015;468675). The Committee considered this evidence indicated some complications of hypophosphatemia were time-related (for example fatigue and/or feeling ill), and while these did not necessarily reflect fracture risk, they would likely appreciably affect people with HHT's quality of life.

8.11.2. The Committee was made aware of a retrospective analysis of data from a broad cohort of 162 hospitalised people receiving FCM that reported that moderate/severe hypophosphatemia was a frequent and persistent adverse drug reaction with FCM requiring treatment and was associated with a longer hospital stay compared with no/mild hypophosphatemia (Fragkos et al. Gastro Hep. 2020;2:205-14). The Committee considered this evidence of an increased cost to the health system associated with moderate/severe hypophosphatemia.

8.11.3. The Committee considered that while some of this evidence was immature, these studies indicated that that people with HHT with iron deficiency could potentially experience quality of life (QOL) impacts from symptoms of both iron deficiency and hypophosphatemia, in addition to the impacts of the underlying HHT disease. The Committee considered it important to avoid compounding symptoms in individuals with a high symptom burden from HHT itself, noting that this group with chronic, frequent blood loss would be expected to become anaemic.

8.12. The Committee was made aware of two predominantly US-based studies (Pierucci et al. Orphanet J Rare Dis. 2012;7:33; Ferry et al. Am J Rhinol Allergy. 2020;34:230-7), each

reporting a prevalence of diagnosed HHT within the range noted in PTAC's previous consideration of this disease. The Committee considered the population-based active surveillance study by Kjeldsen et al. (J Intern Med. 1999;245:31-9) was an appropriate reference for the prevalence estimate of one in 5000 in the general population, given that the study methods were more inclusive than those in other publications reporting HHT prevalence. The Committee considered the prevalence figures might represent an underestimate due to only including those people accessing healthcare. The Committee considered that, on balance, the proportion of people with HHT in New Zealand who were diagnosed as such could be higher than the 10-20% estimated previously, with a low estimate of 15% due to known risk for children of parents with HHT.

8.13. The Committee considered that some people with HHT who are iron deficient with a ferritin of ≤50 mcg/L will quickly experience a decrease in ferritin to ≤20 mcg/L due to ongoing bleeding, although some might be stable at this level and require less frequent iron infusions. However, the Committee considered the rate of movement between those ferritin levels unclear and that recalled previously noting this to be dependent on individual rates of bleeding (PTAC, August 2024). The Committee considered that most, but not all, people with HHT who have ferritin of ≤20 mcg/L would be anaemic. The Committee noted the following evidence on the prevalence of iron deficiency (with or without anaemia) in HHT:

8.13.1. Observational data reporting anaemia in 66% of women with symptomatic HHT; a requirement for IV iron in 41%; IV iron dependence in 26% and transfusion occurrence (not necessarily recurrent) in 42% (Zhang et al. Blood Adv. 2024;8:3166-72).

8.13.2. Cross-sectional data reported by Kasthuri et al. (Am J Hematol. 2017;92:E591-625) in which 50% of 763 consecutive attendees with HHT had a history of iron deficiency anaemia (ever; not current). The Committee considered this was a likely overestimate, and was made aware of a retrospective study reporting that 30% of 717 patients with symptomatic HHT had anaemia (de Gussem et al. J Clin Med. 2020;9:38581).

8.13.3. A prospective single-centre study of 609 people with HHT reported about 30% received iron tablets for iron deficiency anaemia; a similar proportion were iron deficient; and median transferrin saturation and ferritin were 20% and 34 mcg/L (Q1: 18 mcg/L, Q3: 70 mcg/L), respectively (Livesey et al. Thorax. 2012;67:328-33). The Committee considered that this suggested about 65% would have ferritin <50 mcg/L and/or transferrin saturation of <20% and that this aligned with, but was not exactly representative of, the target population in New Zealand. The Committee noted that Shovlin et al. (Plos One. 2014; 9:e88812) reported similar median ferritin and transferrin saturation among 497 HHT patients with pulmonary AVMs.

8.13.4. On balance, the Committee considered it reasonable to estimate that among those with HHT and chronic bleeding in New Zealand, 30% would be anaemic, 65% would have ferritin <50 mcg/L and/or transferrin saturation of <20%, and ~40% (ie this 65% minus about 25%, based on a quarter having ferritin of <18 mcg/L) would have ferritin between 20 and 50 mcg/L.

*Health benefit*

8.14. The Committee considered that there remains no direct comparative evidence for efficacy of FDI versus FCM in people with HHT, however, that there is strong evidence of equivalent iron repletion with FCM and FDI in other conditions and mixed groups. The Committee was made aware of Australian guidance indicating that treatment of iron deficiency without anaemia is reported to improve fatigue in some studies, among other benefits and that this is based mainly on small observational studies (Balendran & Forsyth. Aust Prescr 2021;44:193-6). The Committee considered that there was no new evidence to update the Committee's view that the observational link between iron deficiency with/without anaemia and stroke or VTE in HHT was more than an association.

The Committee focussed its discussion around health benefits on the increased risk of hypophosphatemia associated with repeated use of FCM.

8.15. The Committee noted a systematic review and meta-analysis of 11,700 individuals receiving high-dose IV iron preparations across various therapeutic areas reported overall pooled rates of hypophosphatemia of 47% with FCM and 4% with FDI, and an association between low ferritin or transferrin and hypophosphatemia (Schaefer et al. Br J Clin Pharmacol. 2020;87:2256-73). The Committee noted that the same authors conducted a secondary analysis of two randomised clinical trials in those with iron deficiency anaemia, which only reported an association between hypophosphatemia and the use of FCM (Schaefer, et al. J Clin Endocrinol Metab. 2021;107:1009–19). The Committee noted that the meta-regression in Schaefer et al. 2020 suggested that about half of people with ferritin of 50 mcg/L in that study and about 60% of those with ferritin of 20 mcg/L would have experienced hypophosphatemia.

8.16. The Committee noted a prospectively registered systematic literature review and meta-analysis including 10,467 people with iron deficiency anaemia reported serious or severe hypersensitivity reactions in 1.08% with FCM compared with 0.14% with FDI (Kennedy et al. Int J Clin Pharm. 2023;45:604-12).

8.17. The Committee was made aware of a conference poster presentation of a retrospective cohort study reporting patients treated with FDI experienced reduced fracture incidence (FDI 0.67 fractures per 100 person years versus FCM 1.30) (Pammer et al. poster presentation, American Society of Hematology 2023 annual meeting). The Committee considered this preliminary evidence aligned with the biological plausibility of hypophosphatemia leading to a significantly higher incidence of fractures, and more so with FCM.

8.18. The Committee also noted the current body of evidence regarding the efficacy or quality of life impact of FCM and/or FDI, or hypophosphatemia risk associated with FCM and/or FDI, as provided by the applicants and identified by Pharmac staff.

8.19. The Committee considered the evidence for a reduced incidence of hypophosphatemia with FDI versus FCM from other conditions was strong and that it was reasonable to generalise this evidence to the New Zealand population with HHT. The Committee noted the variable definitions of hypophosphatemia in the literature contributed to its varied reported incidence, but considered it reasonable for Pharmac staff to assume incidence of 47% with FCM and 4% with FDI.

8.20. Overall, the Committee considered that FDI would offer people with HHT the same iron replenishment as FCM but with a reduced risk of harm. The Committee considered that health benefits for family, whānau and wider society would directly relate to reductions in symptomatic hypophosphatemia and its complications.

8.21. The Committee considered that there is moderate quality evidence for treating iron deficiency (without anaemia) with IV iron and achieving symptomatic benefit in other conditions, and acknowledged that this differed from its previous view of this evidence in August 2024. Specifically, the Committee now considered that for people not currently receiving FCM for iron deficiency without anaemia (due to having ferritin >20 mcg/L and ≤50 mcg/L), it was reasonable to assume treatment with FDI would be associated with a reduction in fatigue and other symptoms of iron deficiency.

8.22. The Committee noted that, as described previously, expert opinion and international treatment guidelines advise to treat people with HHT upon iron deficiency, without waiting for anaemia to develop. The Committee considered this to be reasonable and pragmatic, given that anaemia would be expected to occur for this population, and considered it appropriate guidance to align funded access to FDI with for people with HHT.

*Suitability*

8.23. The Committee considered that FDI is likely able to be administered in all settings where FCM is currently administered and no difference in infusion impact on health services would be expected, although it might take some time initially to implement FDI.

8.24. The Committee noted that FDI can be administered at a higher total dose (1500 mg) compared with FCM (1000 mg), although because the clinician applicant had proposed a dose of 1000 mg it was unclear whether the higher dose might be used in practice and therefore whether there would be any reduction in the number of infusions required.

8.25. The Committee considered that with a lower incidence of hypophosphatemia, there would be a lower requirement for monitoring phosphate levels and management.

*Cost and savings*

8.26. The Committee considered that funding as proposed for those with HHT who have iron deficiency could increase the size of the patient group eligible to receive FDI compared with FCM, although it noted that the applicant considered this would enable earlier rather than increased access.

8.27. The Committee considered that high uptake of FDI among those with HHT would be expected, noting many individuals would already be under specialist care and there is a reasonably high awareness among, and support and advocacy for, those with HHT. The Committee considered that FDI would replace most use of FCM in this group, although some individuals might receive FCM infrequently and opt to remain using it only when needed.

8.28. The Committee noted the clinician proposed FDI dosing of 1000 mg of iron every one to three months for individuals with HHT who experience chronic/severe bleeding. The Committee considered that this was reasonable given that there was no evidence to suggest a different dose, although noting expert opinion from the USA suggested it might be used less frequently (for example one to three times per year).

8.29. The Committee considered it was reasonable for Pharmac staff to use evidence from other populations with anaemia and/or hypophosphatemia (such as IBD) to inform the outcomes in its assessment. However, the Committee noted that the bleeding rate in HHT is different to that in other conditions and may be individual-specific, and that some conditions (for instance renal impairment) will influence the risk of developing hypophosphatemia.

8.30. The Committee considered the quality of available evidence was insufficient to confirm resource use with FDI and FCM, although that a reduction in hospitalisation with symptomatic hypophosphatemia was likely. Members considered that Pharmac staff could consider seeking quantifiable information about patient time and comparator costs (for example phosphate testing, noting that this is often ad-hoc) to incorporate into their assessment, if available, which would be more relevant in a lifelong condition like HHT than a transient illness.

*Funding criteria*

8.31. The Committee considered that the funding criteria drafted by Pharmac staff for FDI in the population with HHT, based on the applications, was appropriate to target those who would benefit most.

*General*

8.32. The Committee considered that people with HHT who experience chronic and frequent bleeding would be the most high-need group that would benefit most from FDI compared with FCM. The Committee considered it difficult to define a group(s) with other conditions who might have a similarly high and/or chronic need for an alternative IV iron product with a lower risk of hypophosphatemia than FCM. Members considered that:

8.32.1. Some people with inflammatory bowel disease (IBD) receive regular iron infusions. However, most only require a small number of infusions before iron is stabilised and hypophosphatemia is not often seen in IBD, although members acknowledged that phosphate testing might not occur routinely in this setting. People with intestinal

failure receiving IV iron would undergo phosphate monitoring and receive phosphate when needed.

8.32.2. Those with myelodysplastic syndrome (MDS) who are blood transfusion-dependent for a period of time are at risk of developing hypophosphatemia from aspects of the disease and its direct or supportive treatments. However, the requirement for iron infusions in MDS is unclear given the risk of developing iron overload from transfusions.

8.32.3. Some people with renal failure have iron deficiency associated with chronic disease and are receiving IV iron, but wouldn't be expected to experience hypophosphatemia due to the need for phosphate-lowering medications in the context of renal failure.

8.32.4. Some women with heavy menstrual periods might receive IV iron in primary care.

*Summary for assessment*

8.33. The Committee considered that the below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for FDI if it were to be funded in New Zealand for people with HHT who are iron deficient. This PICO table captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO table is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO table may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

| | |
|---|---|
| Population | People diagnosed with HHT with chronic bleeding resulting in iron deficiency as either:<br>- ferritin of ≤50 mcg/L or<br>- transferrin saturation of ≤20% (with ferritin >50 mcg/L) for occasional patients with an inflammatory state<br><br>Likely to be a bigger group than the individuals who currently receive ferric carboxymaltose at a serum ferritin of ≤20 mcg/L. |
| Intervention | Ferric derisomaltose 1g per infusion given after confirmation of either:<br>- ferritin of ≤50 mcg/L or<br>- transferrin saturation of ≤20% (with ferritin >50 mcg/L)<br><br>Given on an ongoing basis, as often as fortnightly, lifelong as there is no funded disease-modifying therapy. |
| Comparator(s) | Mixed comparator of<br>• No treatment (for those with ferritin >20 mcg/L and ≤50 mcg/L)<br><br>Or<br>• For people with ferritin ≤20 mcg/L, of which most might be anaemic:<br>○ ferric carboxymaltose given in a hospital Emergency Department<br>○ ferric carboxymaltose given in the community<br><br>Likely some iron tablet use.<br><br>Clinician application considers infusion frequency would be the same in the intervention; which will vary between individuals due to the rate of bleeding. |
| Outcome(s) | For patients not currently treated:<br>reduced fatigue and other symptoms of iron deficiency (Balendran & Forsyth. 2021)<br><br>For patients currently treated with FCM:<br>reduced incidence of hypophosphatemia with ferric derisomaltose (iron isomaltoside/ferric derisomaltose [IIM] of 4% versus ferric carboxymaltose 47%) (Schaefer et al. 2020).<br>reduced fractures per 100 person years FCM 1.30, FDI 0.67 (Pammer et al. ASH 2023 annual conference)<br>reduced fatigue associated with hypophosphatemia. (Zoller et al. Gut. 2022;0:1-10)<br>reduced hospitalisation duration. FCM-induced moderate/severe hypophosphatemia associated with a significantly longer hospital stay (Fragkos et al. Value Health. 2021;24(Suppl 1):S230)<br><br>Changes in patients' incidence of bleeding are not expected with this treatment. |
| Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data. | |

## 9. Rituximab for the maintenance treatment of antineutrophilic cytoplasmic antibody associated vasculitis

### Application

9.1. The Committee reviewed the clinician application for rituximab in maintenance treatment of antineutrophilic cytoplasmic antibody (ANCA) associated vasculitis.

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

### Recommendation

9.3. The Committee **recommended** that rituximab for the maintenance treatment of ANCA-associated vasculitis be listed with a **high priority** with no restriction on treatment duration, subject to the following amended Special Authority criteria (additions in **bold**, deletions in ~~strikethrough~~):

RITUXIMAB
Initial application – ANCA-associated vasculitis **(induction and maintenance treatment)**
Application from any relevant practitioner. Approvals valid ~~for 8 weeks~~ **without further renewal unless notified**.

~~All of the following~~ **Both**:

1. Patient has been diagnosed with ANCA-associated vasculitis*; and
2. ~~The total rituximab dose would not exceed the equivalent of 375 mg/m2 of body surface area per week for a total of 4 weeks; and~~
2. Any of the following:
   - 2.1 Induction therapy with ~~daily oral or pulse intravenous~~ cyclophosphamide has ~~failed to achieve~~ **not provided** significant improvement of disease after at least 3 months; or
   - 2.2 Patient has ~~previously~~ had a cumulative dose of cyclophosphamide > 15 g**,** or ~~a further repeat 3 month induction course of cyclophosphamide would result in a cumulative dose > 15 g~~ **or will receive so with a further repeat 3 month induction course;** or
   - 2.3 Cyclophosphamide and methotrexate are contraindicated; or
   - 2.4 Patient is ~~a female~~ of child-bearing potential; or
   - 2.5 Patient has a previous history of haemorrhagic cystitis, urological malignancy or haematological malignancy.

~~Renewal application – ANCA associated vasculitis~~
~~Applications from any relevant practitioner. Approvals valid for 8 weeks.~~
~~All of the following~~:

1. ~~Patient has been diagnosed with ANCA associated vasculitis*; and~~
2. ~~Patient has previously responded to treatment with rituximab but is now experiencing an acute flare of vasculitis; and~~
3. ~~The total rituximab dose would not exceed the equivalent of 375 mg/m2 of body surface area per week for a total of 4 weeks.~~

**Initial application – ANCA-associated vasculitis (maintenance treatment only)**
**Application from any relevant practitioner. Approvals valid without further renewal unless notified.**

**All of the following:**

1. **Patient has been diagnosed with ANCA-associated vasculitis*; and**
2. **Patient has received induction therapy with cyclophosphamide or rituximab; and**
3. **The ANCA-associated vasculitis is in remission.**

* Note: Indications marked with * are unapproved indications.

9.4. In making this recommendation, the Committee considered:

9.4.1. the high health need of people with life or organ threatening ANCA-associated vasculitis and the impact of disease relapses on these people and their families and whānau.

9.4.2. the moderate quality of the available evidence that rituximab reduces the rate of relapse compared to comparator treatment(s) or placebo.

9.4.3. the Committee considered the number of patients enrolled in the key clinical trials was impressive given then rarity of ANCA-associated vasculitis. The Committee considered this provided strong weight to the validity of the outcomes reported.

## Discussion

*Māori impact*

9.5. The Committee discussed the impact of funding rituximab for the maintenance treatment of ANCA-associated vasculitis on Māori health areas of focus | Hauora Arotahi and Māori health outcomes. The Committee considered that while there is no evidence of an increased prevalence of ANCA-associated vasculitis in Māori, there is a concurrent lack of awareness of this condition and lack of research into how this condition impacts Māori.

*Populations with high health needs*

9.6. The Committee discussed the health need(s) of ANCA-associated vasculitis among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs. The Committee discussed the impact of funding rituximab maintenance treatment for ANCA-associated vasculitis and considered:

9.6.1. There may be access barriers to infusions for Māori, Pacific peoples, disabled peoples, and people living in rural areas as well as those experiencing socioeconomic deprivation, which creates cost (both direct and indirect) barriers to accessing care.

*Background*

9.7. The Committee noted that rituximab is already funded for induction treatment of ANCA-associated vasculitis.

9.8. The Committee noted that ANCA-associated vasculitis is an umbrella term that is used to encompass three subgroups of people with the following conditions: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis polyangiitis (EGPA). The Committee considered that EGPA generally has a different treatment regimen, and that these people would be unlikely to use rituximab.

9.9. The Committee noted that ANCA-associated vasculitis is a rare condition with an incidence of 0.4 cases to 24 cases per 1 million person-years. The average age at diagnosis is between 40 years and 50 years of age.

9.10. The Committee noted that New Zealand data (Gibson et al. Rheumatology. 2006;45:624-28) has reported a five-year prevalence of GPA as 152 cases per million and MPA as 58 cases per million. Members were made aware of an unpublished audit (Ravi et al, provided in the applicant submission) indicated an incidence of 9.5 cases of ANCA-associated vasculitis per million with 6% of these people identifying as Māori.

*Health need*

9.11. The Committee noted that ANCA-associated vasculitis is a multi-system chronic condition with no cure, and that the impact of ANCA-associated vasculitis on the quality of life for both the individual and their family and whānau is significant, with frequent hospital and clinic visits being required. The Committee considered that this condition would have an impact on loss of income and productivity in activities of daily living.

9.12. The Committee considered that the intention of maintenance treatment is to prevent relapses and the worse health outcomes associated with them such as cardiovascular and thromboembolic events, renal disease, and irreversible organ damage from necrosis at sites of inflammation.

9.13. The Committee noted that rituximab is currently funded for induction treatment for ANCA-associated vasculitis under Special Authority criteria. The Committee considered that the majority of patients with ANCA-associated vasculitis would be using azathioprine for maintenance treatment, with mycophenolate or methotrexate only being used for patients for whom azathioprine is contraindicated or experiencing intolerance to azathioprine.

9.14. The Committee was made aware of an online survey of acute ANCA-associated vasculitis treatments in Australia and New Zealand (Chua et al. Intern Med J. 2024;54:1097-105). The Committee noted the use of cyclophosphamide as induction therapy was more prevalent than rituximab with only 8% of respondents in New Zealand receiving rituximab as an induction treatment. The Committee considered this could be attributed to limited access to infusion services and prescribing patterns and noted this usage could increase in the future.

*Health benefit*

9.15. The Committee noted the results from the randomised MAINRITSAN trial, which reported rates of major and minor relapse in patients given rituximab fixed dosing or azathioprine taper dosing over 28 months (Guillevin et al. N Engl J Med. 2014;371:1771-80). The Committee noted the reported rates of major relapse were 5% in the rituximab arm compared with 29% in the azathioprine arm. The Committee noted the reported rates of minor relapse were 11% in the rituximab arm and 16% in the azathioprine arm.

9.15.1. The Committee noted patients enrolled in the MAINRITSAN trial were either newly diagnosed (80%) or in remission after relapse (20%).

9.15.2. The Committee noted that the reported hazard ratio (HR) of 6.61 for major relapse by month 28 (95% confidence interval [CI] 1.56, 27.96) related to azathioprine's events when compared with rituximab's. The Committee considered that for the purposes of this proposal (rituximab) the relevant comparison would mean a HR of 0.15 for major relapses with rituximab compared with azathioprine at 28 months, being the inverse of the published HR (azathioprine vs rituximab).

9.16. The Committee noted the results from the long-term efficacy study of patients in the MAINRITSAN trial that followed patients from month 28 to month 60 after receiving 18 months maintenance treatment (Terrier et al. Ann Rheum Dis. 2018;77:1151-7). The Committee considered this extension study was observational and only followed 68 patients. The Committee noted the reported major relapse-free survival rates at month 60 were 71.9% in the rituximab arm (CI 38%, 64.3%) and 49.4% in the azathioprine arm (CI 61.2%, 84.6%).

9.17. The Committee noted the results from the open-label, randomised MAINRISTAN2 trial that reported number of relapses by month 28 in patients receiving tailored rituximab dosing compared to fixed rituximab dosing (Charles et al. Ann Rheum Dis. 2018;77:1144-50). The Committee noted the reported relapses in the tailored dosing arm was 17% compared to the fixed dosing arm at 10%. The Committee noted that the difference between the two arms was not reported to be statistically significant.

9.18. The Committee noted the results from the double-blind, randomised MAINRITSAN3 clinical trial that reported relapse-free survival after 28 months in patients receiving fixed dose rituximab maintenance treatment or placebo (Charles et al. Ann Int Med. 2020;173:179-87). The Committee noted that patients in remission after completing MAINRITSAN2 were randomised to either further rituximab treatment or placebo. The Committee noted the reported relapse-free survival rates were 96% in the rituximab arm and 74% in the placebo arm. The Committee noted the reported HR of 7.5 (CI 1.67, 33.7) at 28 months was for the risk of relapse or death.

9.19. The Committee considered that the treatment duration and dosing intervals for rituximab maintenance treatment for ANCA-associated vasculitis should not be restricted and that it should remain the purview of the treating clinician to determine the appropriate duration of treatment. The Committee considered that clinicians would refer to international guidelines on dosing which recommend maintenance treatment for 24 to 48 months.

9.20. The Committee noted the results from the randomised open label RITAZAREM trial that reported rates of relapses at month 24 in patients receiving rituximab or azathioprine (Smith et al. Ann Rheum Dis 2023;82:937-44). The Committee noted the rituximab dosing was higher in this trial (1g per dose) compared to previous clinical trials (500mg per dose i.e. Terrier et al. 2018). The Committee considered this was reasonable given the patient

cohort in RITAZAREM were all previously relapsed and considered higher risk. The Committee noted that at month 24, the relapse-free survival rate was 0.85 (95% CI 0.78,0.93 for the rituximab compared with 0.61 (0.51,0.73) for the azathioprine groups (Smith et al. 2023).

9.21. The Committee considered the number of patients enrolled in the key clinical trials was impressive given then rarity of ANCA-associated vasculitis. The Committee considered this provided strong weight to the validity of the outcomes reported.

9.22. The Committee noted similar rates of adverse events for patients on rituximab and azathioprine in both MAINRITSAN and RITAZAREM trials.

9.23. The Committee noted that all the clinical trials reviewed used the Birmingham Vasculitis Activity Score (BVAS) as a measure of defining remission or relapse. In Smith et al. 2023 this tool was also referred to as Wegeners Granulomatosis WG and noted as BVAS/WG. The Committee noted that this scoring system is an objective marker of disease used internationally and incorporates signs and symptoms of disease impact reported by both the patient and clinician (Flossmann et al. Ann Rheum Dis. 2007;66:283-92). The Committee considered, however, that the BVAS scoring system is unlikely to be widely used in clinical practice for determining severity of disease.

9.24. The Committee noted that the key clinical trials considered did not report on hospitalisation rates but considered that relapse rates are likely to correlate with hospitalisation rates because patients would require medical treatment to manage relapses. The Committee noted that higher rates of end stage kidney disease would also correlate with greater health resource utilisation and lower quality of life dependent on the person's situation.

9.25. The Committee noted that patients whose disease relapsed while on maintenance treatment would be reinduced with rituximab and would likely receive the same level of benefit for maintaining remission.

*Suitability*

9.26. The Committee noted rituximab is administered as an infusion, generally in an outpatient setting. The Committee considered that widening access to rituximab would increase pressures on infusion services.

9.27. The Committee considered some people in priority populations (for instance Māori, Pacific peoples) may be disadvantaged and not be able to access rituximab maintenance treatment. The Committee considered that these people would generally still have the option of oral maintenance treatment with azathioprine, mycophenolate or methotrexate, although with lesser efficacy compared to rituximab.

*Cost and savings*

9.28. The Committee noted that the cost of rituximab maintenance treatment would also have associated costs to the health sector with regard to infusion costs.

9.29. The Committee considered that, after noting the efficacy of rituximab compared to current standard treatment from the clinical trials discussed, treatment with rituximab would reduce the rate of relapse in patients in remission with ANCA-associated vasculitis. The Committee considered this could result in associated savings related to healthcare costs and costs to the community and whānau due to relapse.

9.30. The Committee considered it appropriate to assume the majority of patients would currently be receiving azathioprine, with patients for whom azathioprine was contraindicated receiving a split of mycophenolate or methotrexate.

9.31. The Committee considered Pharmac's estimate of people who would receive rituximab maintenance therapy reasonable, given the outlined NZ prevalence rates. The Committee noted it is reasonable to assume a high uptake rate for rituximab maintenance therapy due to the significantly lower relapse rates.

*Funding criteria*

9.32. The Committee considered that the listing of rituximab for maintenance treatment of ANCA-associated vasculitis should be subject to the following Special Authority criteria.

RITUXIMAB
Initial application – ANCA-associated vasculitis (induction and maintenance treatment)
Application from any relevant practitioner. Approvals valid without further renewal unless notified.
Both:
1. Patient has been diagnosed with ANCA-associated vasculitis*; and
2. Any of the following:
    2.1 Induction therapy with cyclophosphamide has not provided significant improvement of disease after at least 3 months; or
    2.2 Patient has had a cumulative dose of cyclophosphamide > 15 g, or will receive so with a further repeat 3-month induction course**;** or
    2.3 Cyclophosphamide-and methotrexate are contraindicated; or
    2.4 Patient is of child-bearing potential; or
    2.5 Patient has a previous history of haemorrhagic cystitis, urological malignancy or haematological malignancy.

Initial application – ANCA-associated vasculitis (maintenance treatment only)
Application from any relevant practitioner. Approvals valid without further renewal unless notified.
All of the following:
1. Patient has been diagnosed with ANCA-associated vasculitis*; and
2. Patient has received induction therapy with cyclophosphamide or rituximab; and
3. The ANCA-associated vasculitis is in remission.

* Note: Indications marked with * are unapproved indications.

9.33. The Committee considered that the criterion in multiple Special Authority forms regarding patients being of childbearing potential should be revised to preserve reproductive potential in all patients (all genders).

9.34. The Committee considered that due to the variation in treatment duration in the clinical trials, duration should not be limited by the Special Authority and approvals should be valid without further renewal.

*General discussion*

9.35. The Committee considered the benefit of removing all Special Authority restrictions for rituximab and having this open listed on the Pharmaceutical Schedule. The Committee considered that removing this barrier to access treatment would benefit patients and clinicians, particularly those with rare disorders or indications that are not funded through the Special Authority. The Committee considered that these patients are currently relying on clinicians submitting Named Patient Pharmaceutical Assessment (NPPA) applications on their behalf and this process is highly resource intensive for the clinician.

9.36. The Committee considered the risks of removing all Special Authority restrictions for rituximab may include unknown financial increase with wider access, inappropriate dosing regimens, and limited access to infusion centres resulting in inequitable access to treatment.

9.37. The Committee noted that the current formulation of rituximab is a chimeric monoclonal antibody which is associated with a risk of infusion reactions. The Committee considered that there may be a fully humanised version of rituximab developed in the future which has the same efficacy for treatment but with less adverse events. The Committee considered this may pose a challenge for Pharmac if this product came at a higher cost and rituximab was listed without restriction on the Pharmaceutical Schedule.

*Summary for assessment*

9.38. The Committee considered that the below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for rituximab if it were to be funded in New Zealand for maintenance treatment of ANCA-associated vasculitis. This PICO table captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO

table is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO table may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

| | |
|---|---|
| **P**opulation | People with ANCA-associated vasculitis who have had life or organ threatening disease and have received induced remission from corticosteroids AND rituximab and/or cyclophosphamide if previous treatment failure on either agent. |
| **I**ntervention | Rituximab 500 mg on day 0 and 14, then 500 mg every six months until relapse. |
| **C**omparator(s) (NZ context) | Majority of treated individuals:<br>• azathioprine 2mg/kg/day at complete remission until month 12, decreasing to 1.5mg/kg/day until month 18, then 1mg/kg/day until month 22.<br><br>Individuals contraindicated to azathioprine:<br>• mycophenolate mofetil 2000 mg/day (divided doses) for 2 years.<br>• methotrexate 0.3 mg per kilogram per week, progressively increased to 25 mg per week. |
| **O**utcome(s) | *Reduction in rate of major or minor relapse*<br>• MAINRITSAN reported that rituximab was associated with a reduction in the rate of major and minor relapses compared to azathioprine (adjusted HR, 0.31 [95% CI 0.18 to 0.53]) (Delestre et al. Annals of Rheum. 2024;83:233-41).<br><br>*Reduction in rate of major relapse*<br>• MAINRITSAN reported that rituximab was associated with a reduction in the rate of major relapses compared to azathioprine (adjusted HR, 0.38 [95% CI 0.20 to 0.71]) (Delestre et al. 2024). |
| *Table definitions:*<br>**P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)<br>**I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).<br>**C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).<br>**O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data. | |

## 10. Nivolumab with ipilimumab for unresectable malignant mesothelioma

### Application

10.1. The Committee reviewed the application for nivolumab with ipilimumab for the treatment of surgically unresectable malignant mesothelioma.

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 nivolumab with ipilimumab for the treatment of malignant pleural mesothelioma of the sarcomatoid or biphasic subtypes be listed with a **medium priority,** subject to the following Special Authority criteria:

NIVOLUMAB
**Initial application** – Applications only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:
1. Person has malignant pleural mesothelioma; and
2. Person has sarcomatoid or biphasic histology and
3. Person has ECOG performance status 0-2; and

4. Person has not received any previous treatment for their malignant pleural mesothelioma; and
5. The treatment must be in combination with subsidised ipilimumab, unless an intolerance to ipilimumab of a severity necessitating permanent treatment withdrawal of ipilimumab; and
6. Baseline measurement of overall tumour burden is documented clinically and radiologically; and
7. Nivolumab to be used at a maximum dose of either 3 mg/kg every two weeks or 360 mg every three weeks (or equivalent).

**Renewal application** – Applications only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:
1. Any of the following:
   1.1. Person's disease has had a complete response to treatment; or
   1.2. Person's disease has had a partial response to treatment; or
   1.3. Person has stable disease; and
2. Response to treatment in target lesions has been determined by comparable radiologic assessment following the most recent treatment period; and
3. Nivolumab to be used at a maximum dose of either 3 mg/kg every two weeks or 360 mg every three weeks (or equivalent); and
4. Maximum treatment period of 24 months (cumulative total of initial plus renewed treatments).

IPILIMUMAB
**Initial application** – Applications only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:
1. Person has malignant pleural mesothelioma; and
2. Person has sarcomatoid or biphasic histology and
3. Person has ECOG performance status 0-2; and
4. Person has not received any previous treatment for their malignant pleural mesothelioma; and
5. The treatment must be in combination with subsidised nivolumab; and
6. Baseline measurement of overall tumour burden is documented clinically and radiologically; and
7. Ipilimumab to be used at a maximum dose of 1 mg/kg every six weeks (or equivalent).

**Renewal application** –. Applications only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:
1. Any of the following:
   1.1. Person's disease has had a complete response to treatment; or
   1.2. Person's disease has had a partial response to treatment; or
   1.3. Person has stable disease; and
2. Response to treatment in target lesions has been determined by comparable radiologic assessment following the most recent treatment period; and
3. Ipilimumab to be used at a maximum dose of 1 mg/kg every six weeks (or equivalent); and
4. Maximum treatment period of 24 months (cumulative total of initial plus renewed treatments).

10.4. The Committee **recommended** that nivolumab with ipilimumab for the treatment of malignant pleural mesothelioma (any subtype) be listed with a **low priority,** subject to the following Special Authority criteria:

NIVOLUMAB
**Initial application** – Applications only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:
1. Person has malignant pleural mesothelioma; and
2. Person has ECOG performance status 0-2; and
3. Person has not received any previous treatment for their malignant pleural mesothelioma; and
4. The treatment must be in combination with subsidised ipilimumab, unless an intolerance to ipilimumab of a severity necessitating permanent treatment withdrawal of ipilimumab; and
5. Baseline measurement of overall tumour burden is documented clinically and radiologically; and
6. Nivolumab to be used at a maximum dose of either 3 mg/kg every two weeks or 360 mg every three weeks (or equivalent)

**Renewal application** – Applications only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:
1. Any of the following:

1.1. Person's disease has had a complete response to treatment; or
1.2. Person's disease has had a partial response to treatment; or
1.3. Person has stable disease; and

2. Response to treatment in target lesions has been determined by comparable radiologic assessment following the most recent treatment period; and
3. Nivolumab to be used at a maximum dose of either 3 mg/kg every two weeks or 360 mg every three weeks (or equivalent); and
4. Maximum treatment period of 24 months (cumulative total of initial plus renewed treatments).

IPILIMUMAB
**Initial application** – Applications only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:
1. Person has malignant pleural mesothelioma; and
2. Person has ECOG performance status 0-2; and
3. Person has not received any previous treatment for their malignant pleural mesothelioma; and
4. The treatment must be in combination with subsidised nivolumab; and
5. Baseline measurement of overall tumour burden is documented clinically and radiologically; and
6. Ipilimumab to be used at a maximum dose of 1 mg/kg every six weeks.

**Renewal application** –Applications only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:
1. Any of the following:
1.1. Person's disease has had a complete response to treatment; or
1.2. Person's disease has had a partial response to treatment; or
1.3. Person has stable disease; and
2. Response to treatment in target lesions has been determined by comparable radiologic assessment following the most recent treatment period; and
3. Ipilimumab to be used at a maximum dose of 1 mg/kg every six weeks (or equivalent); and
4. Maximum treatment period of 24 months (cumulative total of initial plus renewed treatments).

10.5. The Committee considered the following when making these recommendations:

10.5.1. the very high health needs of people with malignant mesothelioma, often associated with occupational exposure to asbestos, in particular, the non-epithelioid subtypes (sarcomatoid and biphasic) which have a poorer prognosis

10.5.2. the improved health outcomes from nivolumab with ipilimumab, particularly for the non-epithelioid subtype of mesothelioma, as reported in pivotal clinical trials

10.5.3. there is insufficient evidence supporting nivolumab with ipilimumab for the treatment of non-pleural malignant mesotheliomas, regardless of location of the mesothelioma, such as abdominal, pericardial and testicular mesotheliomas, in the context of the rarity of non-pleural forms of the disease rendering such evidence difficult to obtain

10.5.4. the evidence provided and available supports the use of nivolumab with ipilimumab for the first line treatment of mesothelioma. The Committee's consideration was in the context of first line treatment only, however access to nivolumab with ipilimumab for previously treated people could be a future consideration for the Cancer Treatments Advisory Committee.

## Discussion

*Māori impact*

10.6. The Committee discussed the impact of funding nivolumab and ipilimumab for the treatment of malignant mesothelioma on Māori health areas of focus | Hauora Arotahi and Māori health outcomes. Romaha ora | respiratory health is one of these areas. The Committee noted Māori are not overrepresented in malignant mesothelioma diagnoses.

*Populations with high health needs*

10.7. The Committee discussed the health need(s) of those with malignant mesothelioma among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs. The Committee discussed the impact of funding nivolumab and ipilimumab, and noted:

10.7.1. based on the latest data available from the Health NZ Cancer Web Tool, which uses the NZ Cancer Registry as its primary data source, NZ European/Other had the highest cumulative incidence of all mesothelioma (C45) cancer registrations with 1.2 cases per 100,000 people between 2018 and 2022, noting that this rate is standardised to the World Health Organization's standard world population. Māori had a cumulative 5-year incidence over this period of 1.0 cases per 100,000 population, while Pacific people had a rate of 0.49 and Asian 0.28 cases per 100,000 respectively (Health NZ Cancer web tool, registrations for C45 mesothelioma for the years 2018 to 2022)

10.7.2. malignant mesothelioma registrations are more common in men than women (seen in the 5-year cumulative incidence between 2018 and 2022, which were 1.76 versus 0.3 per 100,000 for Māori males and Māori females, and 2.21 vs 0.33 for males and females of NZ European/Other ethnicity) (taken from the Health NZ Cancer Web Tool). Data for other ethnic groups were insufficient to make inferences

10.7.3. there is a relatively equal spread of disease across socioeconomic deprivation indicators, 5-year cumulative registrations ranging between 0.98 and 1.28 per 100,000 across the five NZDepIndex quintiles (Health NZ Cancer Web Tool).

*Background*

10.8. The Committee noted that in addition to malignant mesothelioma, Pharmac was also currently assessing nivolumab with ipilimumab for the following indications.

10.8.1. metastatic kidney cancer with a clear cell component, with poor, intermediate and favourable International metastatic RCC Database Consortium IMDC risk prognoses, as first line therapy

10.8.2. advanced non-small cell lung cancer, as first line combination therapy, irrespective of PDL-1 status

10.8.3. malignant melanoma, as either surgically unresectable or metastatic.

10.9. The Committee noted that people who have malignant mesothelioma due to asbestos exposure are also currently eligible to access nivolumab with ipilimumab and other treatments through the Accident Compensation Corporation (ACC) pathway. In 2021/22 there were 83 accepted claims, and in 2022/23, there were 62 accepted claims for mesothelioma (where payments were not limited to cancer treatments including nivolumab with ipilimumab).

*Health need*

10.10. The Committee noted that mesothelioma is a cancer affecting the mesothelial cells which cover most internal organs. Approximately 90% of all cases are pleural, 2% are abdominal, 1% are pericardial, but there are other forms dependent on where it occurs in the body (AIHW 2023, Bridda et al. MedGenMed. 2007;109:32; Mensi et al. Int J Hyg Environ Health. 2011;214:276-9). The Committee noted that testicular mesothelioma is extremely rare.

10.11. The Committee noted that mesotheliomas can be further disaggregated according to histological subtype, being classified as epithelioid, sarcomatoid or biphasic. Members noted the prognosis is variable, however malignant mesothelioma that has epithelioid histology has a better prognosis (Sugarbaker et al. J Clin Oncol. 1993;11:1172-8). However mesotheliomas with positive lymph node involvement, indicating spread, is associated with poorer survival than those without lymph node involvement. People with

epithelial variants and negative mediastinal lymph node involvement had the highest survival rate of 45% at 5 years (Sugarbaker et al. 1993).

10.12. The Committee noted that malignant mesothelioma is non-curable, but treatment may prolong survival. With no treatment, survival is approximately 6 to 9 months from diagnosis (Nief et al. Clin Lung Cancer. 2023;24:76-81). The Committee noted pemetrexed-containing chemotherapy is funded and this is associated with median survival extending to approximately 14 (95% CI 11,17) months for pleural mesothelioma, while radical surgery plus chemotherapy can extend median survival to 31 (95% CI 28,45) months for peritoneal mesothelioma (Amin et al. F1000Res 2018;7:1184). However, the Committee noted that radical surgery can be significantly debilitating due to the intensive nature of the procedure.

10.13. The Committee noted that a major risk factor for malignant mesothelioma is exposure to asbestos, however better exposure control from protective measures and using different building products around the world has resulted in declining incidence rates (Mott FE. Ochsner J. 2012;12:70-9).

10.13.1. The Committee noted incidence rates are slightly increasing in women (Stevens et al. Toxicol Ind Health. 2024;41:40-60) and considered this could be due to environmental exposure rather than occupational exposure to asbestos, in addition to exposure to other mineral fibres in the person's neighbourhood.

10.13.2. Approximately 1% of cases are associated with germline mutations/deletions in the BRCA-1 associated protein (Rusch et al. Lung Cancer. 2015;87:77-9).

10.14. The Committee considered that global incidence rates are complicated by increasing migration and exposure prior to migration. There is usually a 20 to 40 year lag period between exposure to asbestos and the disease manifesting (Huang et al. JTO. 2023;18:792-802). The Committee considered that forecasts of future patient numbers would need to account for immigration from countries with higher rates of asbestos exposure.

10.15. The Committee noted that malignant mesothelioma is often diagnosed at an advanced stage, as the early signs and symptoms are subtle (Bibby et al. Eur Respir Rev. 2016;25:472-86).

10.16. The Committee noted that the current funded treatment options include:

- chemotherapy, usually with pemetrexed with a platinum-containing agent
- radiotherapy for pleural mesothelioma only
- peritonectomy combined with hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal epithelioid type mesothelioma.

10.17. The Committee considered there is minimal to no radical surgery used in New Zealand to treat mesothelioma. The Committee noted the Mesothelioma and Radical Surgery (MARS) study (Treasure et al. Lancet Oncol. 2011;12:763-72), which reported worse outcomes with radical surgery for pleural mesothelioma in comparison to either chemotherapy or no treatment at all. The Committee considered this was due to the radical nature of the surgery, which results in significant morbidity leading to no survival advantage. The Committee noted these results were further supported by a 2024 study (Lim et al. Lancet Respir Med.2024;12:457-66), which examined radical surgery with or without chemotherapy.

10.18. The Committee noted that in New Zealand, some cases of abdominal mesothelioma, such as those with epithelioid morphology that satisfy other clinical considerations, are often treated by HIPEC which is available in both Auckland and Waikato. The Committee noted there are very low volumes of cases treated in this manner, and identified that Waikato has had eleven cases in thirteen years, whilst Auckland has had four cases in six years.

10.19. Overall, the Committee noted that all the studies reviewed indicated extremely poor quality of life associated with malignant mesothelioma.

*Health benefit*

10.20. The Committee noted that nivolumab and ipilimumab are immune checkpoint inhibitors that are different and complementary in action. Nivolumab is a human anti-programmed cell death (PD-1) antibody, while ipilimumab human anti-cytotoxic T-lymphocyte (CTLA-4) antibody. Both nivolumab and ipilimumab are approved by Medsafe to be administered in combination for the first line treatment of surgically unresectable pleural malignant mesothelioma, amongst other indications.

10.21. The Committee noted that nivolumab with ipilimumab is currently funded:

10.21.1. in Australia from 2021 for pleural and non-pleural mesothelioma. The Committee noted non-pleural mesothelioma was included due to low numbers

10.21.2. in Canada from 2021, for pleural mesothelioma only. The Committee noted a price reduction of 72% was required to reach acceptable levels of cost-effectiveness

10.21.3. in Scotland in 2022 for pleural mesothelioma only

10.21.4. in England and Wales in 2022 for pleural mesothelioma only. Cost-effectiveness estimates were within an acceptable range because it was considered a life extending treatment at the end of life.

10.22. The Committee noted the results of the three-year follow up data from CheckMate 743, a multicentre, randomised, open label, phase 3 trial comparing nivolumab with ipilimumab to platinum based chemotherapy in surgically unresectable pleural mesothelioma (Peters et al. Ann Oncol. 2022;33:488-99).

10.22.1. The Committee noted the study was originally planned to report progression free survival (PFS), but after discussion with the Federal Drug Agency (FDA), the primary endpoint was changed to overall survival (OS). The Committee noted the reported subgroup analysis was planned prospectively.

10.22.2. The Committee noted that the study population was confined to people with pleural mesothelioma only, and did not consider that this evidence would apply to other sites of mesothelioma.

10.22.3. The Committee noted that the study population was confined to previously untreated people and considered that evidence from the CheckMate 743 trial would be insufficient to model efficacy in previously treated people.

10.22.4. The Committee considered baseline patient characteristics were similar across both arms.

10.22.5. The Committee noted that study reported the median OS was 18.1 months with nivolumab plus ipilimumab versus 14.1 months with chemotherapy (HR 0.73, 95% CI 0.61,0.87). Similarly, median 3-year OS rates were 23.2% versus 15.4% respectively.

10.22.6. The Committee noted the study did not report a statistically significant difference in PFS, with a median of 6.8 months with nivolumab plus ipilimumab versus 7.2 months with chemotherapy (HR 0.92,95% CI 0.76,1.11). The Committee therefore considered that it would not be appropriate to model a PFS benefit based on this data.

10.22.7. The Committee noted that participants in this study had good ECOG performance (for example ECOGs of 0 for 242 people) with a median age of 69 years, but considered that this would not reflect the New Zealand clinical setting, where patients are usually older and with poorer functional performance.

10.22.8. The Committee noted that only 20% of participants were aged 75 years or older, and this group did not appear to benefit from immunotherapy in subgroup analysis (although acknowledging that no results from any testing for statistical heterogeneity were reported, thus Members were unable to exclude the trial's positive effect overall applying to this subgroup too). The Committee considered there was a risk that the benefit could be overestimated while underestimating

harm, as those receiving treatment in the New Zealand population clinical setting would likely be at least 75 years of age, which is older than the study population (where e.g. 56% of mesothelioma registrations in 2022 were aged 75+ years and over (Health NZ Cancer Web Tool), compared with the 69-year median in the trial).

10.22.9. The Committee noted the mean and median duration of treatment was six to nine months, and only 8% of participants received two years of treatment.

10.22.10. The Committee noted the study reported an OS of 68% versus 58% in the chemotherapy group at 1 year. The Committee considered the difference in OS may have been due to the benefits observed in the sarcomatoid and biphasic subgroups (HR 0.46, 95% CI 0.31,0.68), which reported a greater OS gain compared to the epithelioid subgroup which reported no statistically significant difference in OS (HR 0.86, 95% CI 0.69,1.08). The Committee noted the sarcomatoid and biphasic subgroups had worse prognoses at baseline, and therefore considered the results were clinically significant.

10.22.11. The Committee noted that in the chemotherapy group there was less discontinuation due to disease progression (16%) and due to drug toxicity (8%). More than 50% of participants completed the full regimen (62%). 20% received subsequent immunotherapy, however there was a wide range of immunotherapy, not just nivolumab and ipilimumab.

10.22.12. The Committee noted that there were more treatment related events in the immunotherapy group (21% vs 8%), and this difference was consistent across grade 3 or 4 treatment related events (15% vs 6%). The Committee considered this difference to be clinically significant.

10.22.13. The Committee noted the most common adverse effect in the immunotherapy group was diarrhoea and for chemotherapy it was nausea. There were three treatment related deaths in the immunotherapy group (due to pneumonitis, encephalitis and heart failure) and one in the chemotherapy group (due to myelosuppression).

10.22.14. The Committee considered the greatest risk of disease progression is very early on in treatment. The Committee considered the increase in treatment related adverse events could lead to treatment being discontinued early, which would increase the risk of rapid progression.

10.22.15. The Committee noted there was no difference in health-related quality of life from patient-reported outcomes between treatment arms, and therefore considered it would be inappropriate to include such a benefit in Pharmac's assessment of this proposal

10.22.16. The Committee considered the CheckMate 743 results to be relevant to the New Zealand population, as the trial included patients from Australia and there were no data to suggest that different groups or populations would benefit differently to treatment

10.23. The Committee noted the efficacy results of a retrospective multicentre case series of Latin American mesothelioma patients treated with nivolumab with ipilimumab in a first line setting (Enrico et al. Clin Lung Cancer. 2024;25:723-31). There were 96 patients from across 15 centres, over a seven-year period, with no comparator. 78% of patients had mesothelioma of the epithelioid subtype, and 81% were ECOG 0-1. The study reported a median OS of 22 months (95% CI, 18.9-25), which authors reported to be comparable to that of the pivotal trial.

10.24. The Committee noted results from an observational efficacy and safety study, where patients with untreated, surgically unresectable, pleural mesothelioma were treated with nivolumab plus ipilimumab. This was a French, multicentre retrospective case series of two thirds (n=201) of 305 patients enrolled through an Early Access Programme. These 201 patients were followed over a median 18-month period. There was no comparator

group, and the median OS was 18.9 months in this subset of patients (Bylicki et al. Lung Cancer. 2024:194:107866).

10.25. The Committee noted an Australian retrospective non-comparative study of 119 patients across 11 centres, examining the toxicity of and overall survival with combination immunotherapy for pleural mesothelioma in a first line setting. The median age was 72 years, and nivolumab plus ipilimumab were administered to 75% of patients. The study reported a median OS of 14.5 months, with 24% of patients experiencing an adverse event, including three deaths (McNamee et al. J Thorac Oncol. 2024;19:636-42).

10.25.1. The Committee considered this study to be more reflective of results expected in the New Zealand clinical setting than the Checkmate 743 trial, as there was generally more toxicity and poorer survival outcomes at baseline.

10.26. The Committee noted that the application was for nivolumab with ipilimumab for the treatment of any malignant mesothelioma (all sites). However, the Committee considered that the evidence available only pertained to a benefit for pleural mesothelioma. The Committee noted nivolumab and ipilimumab are also only approved by Medsafe for the treatment of pleural mesothelioma. The Committee considered that the evidence supporting efficacy of nivolumab in combination with ipilimumab in pleural mesothelioma from the Checkmate 743 study cannot be extrapolated to other forms of mesothelioma.

10.27. The Committee considered that the CheckMate 743 study overall was of medium (good) quality in a setting unlikely to get better. The Committee considered the study supported the likelihood of a health benefit in treating all pleural mesothelioma, however, that this benefit was likely driven by superior outcomes in sarcomatoid and biphasic subtypes.

10.28. Members were made aware of signals (for example Scherpereel et al. Lancet. Oncol. 2019;20:239-53; Disselhorst et al. Lancet Respir Med. 2019;7:260-70) that treatment with nivolumab with ipilimumab in previously treated mesothelioma (ie. second or later lines) may provide some ongoing benefit in recurrent disease. Members considered that it may be reasonable to explore access to nivolumab in combination with ipilimumab for previously-treated individuals (ie. beyond first-line treatment), but further consideration of the health benefits from its use in subsequent lines would be needed.

*Suitability*

10.29. The Committee noted that nivolumab is administered according to weight-based dosing fortnightly or a flat-fixed dose of 360 mg every three weeks The Committee considered that in New Zealand we were more likely to use flat-fixed dosing (ie standard dosing without correction for body size or other (pharmacological) parameters). Ipilimumab is given at a weight-based dose every six weeks. The Committee noted that treatment could continue for up to two years, compared to six cycles of platinum-pemetrexed chemotherapy which usually occurs every three months (ie usually 18 months total). The Committee considered this would have an additive impact on infusion capacity in New Zealand.

10.30. The Committee considered that if nivolumab and ipilimumab were funded for malignant mesothelioma, there would be more specialist and primary care appointments to monitor the disease and manage any associated adverse events.

*Cost and savings*

10.31. The Committee considered that Pharmac staff estimate of approximately 106 incident patients per year appeared reasonable. Members considered that all (100%) of these would have disease that was surgically unresectable, and that approximately 70% were likely to have ECOG 0-1 performance.

10.32. The Committee considered there would likely be 100% uptake, considering clinician comfort with immunotherapy and its existing access through ACC.

10.33. The Committee noted an increase in treatment time with nivolumab plus ipilimumab in comparison to the current standard of care, which is platinum-pemetrexed chemotherapy

for six months, will require more infusion time and associated increases in healthcare utilisation costs.

10.34. The Committee considered flat-fixed dosing rather than weight-based dosing for nivolumab is more likely to be used in New Zealand.

10.35. The Committee considered there would be additional costs to manage adverse events associated with immunotherapy compared to chemotherapy.

*Funding criteria*

10.36. The Committee considered that funding should be restricted to first line treatment of pleural mesothelioma only, as the available evidence supports use only in this type. The Committee considered the current available evidence was probably insufficient to support the use of nivolumab with ipilimumab beyond first line treatment at this time, however further consideration would be required.

10.37. The Committee considered that it would be redundant to specify or require surgical non-resectability in any funding eligibility criteria, given the minimal use of surgery as mainstay treatment for pleural mesothelioma in New Zealand.

10.38. The Committee noted the mean and median duration of treatment in the pivotal CheckMate 743 trial was six to nine months and only 8% of participants received two years of treatment. However, the Committee considered that treatment should be available for up to 24 months, in line with the trial data.

10.39. The Committee considered there to be a population that is currently accessing nivolumab with ipilimumab already through ACC, where it is estimated that approximately 75% of these cases would be of epithelioid histology.

*Summary for assessment*

10.40. The Committee considered that the below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for nivolumab and ipilimumab if it were to be funded in New Zealand for malignant mesothelioma. This PICO table captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO table is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO table may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

| | | |
|---|---|---|
| **P**opulation | Treatment-naïve individuals with malignant pleural mesothelioma of any subtype | Treatment-naïve individuals with malignant pleural mesothelioma **with sarcomatoid or biphasic subtype** |
| **I**ntervention | • nivolumab 360 mg q3w<br>• ipilimumab 1 mg/kg q6w | |
| **C**omparator(s)<br>(NZ context) | First line treatment with platinum-based chemotherapy<br>(as per clinical management guidelines, the recommendation is a combination chemotherapy containing pemetrexed and a platinum compound (cisplatin or carboplatin) with or without concomitant corticosteroids) | |
| **O**utcome(s) | • longer overall survival by 4.0 months (hazard ratio 0.74 [96.6% CI 0.60,0.91])<br>• increased rate of adverse events | • longer overall survival by 9.3 months (hazard ratio 0.46 [95% CI 0.31,0.68])<br>• increased rate of adverse events |
| Table definitions:<br>Population, the target population for the pharmaceutical;<br>Intervention, details of the intervention pharmaceutical;<br>Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care);<br>Outcomes, details the key therapeutic outcome(s) and source of outcome data. | | |

## 11. Liraglutide for weight loss

### Application

11.1. The Committee reviewed the application for liraglutide in the treatment of weight management of:

11.1.1. individuals with a BMI of 55kg/m$^2$ and over, with high cardiovascular risk, without type two diabetes mellitus (T2DM), and unable to access publicly funded bariatric surgery

11.1.2. Māori and/or Pacific people with BMI 50kg/m$^2$ and over, with high cardiovascular risk, without T2DM

11.2. In addition, the Committee's views were sought on the GLP-1 agonist class of agents in general for weight management, including which groups of people and/or clinical circumstances might have the greatest need and/or greatest potential for treatment benefit.

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

### Recommendation

11.4. The Committee **recommended** that liraglutide in the weight management of either (1) individuals with a body mass index (BMI) 55kg/m$^2$and over, with high cardiovascular risk, without type two diabetes mellitus (T2DM), unable to access publicly-funded bariatric surgery; or (2) Māori and/or Pacific people with BMI 50kg/m$^2$and over, with high cardiovascular risk, without T2DM, be funded with a **low priority** subject to the following Special Authority criteria:

Initial application – Obesity
Applications from any relevant practitioner. Approvals valid for 12 months.
Either:

1. All of the following:
   - 1.1. Patient is obese with a BMI ≥55 kg/$m^2$; and
   - 1.2. Patient is unable to qualify for publicly-funded bariatric surgery; and
   - 1.3. Patient does not have type 2 diabetes; and
   - 1.4. Patient has pre-existing cardiovascular disease or high cardiovascular risk (see notes a and b); or
2. All of the following:
   - 2.1. Patient is of Māori or Pacific ethnicity; and
   - 2.2. Patient is obese with a BMI of ≥50 kg/$m^2$; and
   - 2.3. Patient does not have type 2 diabetes; and
   - 2.4. Patient has pre-existing cardiovascular disease or high cardiovascular risk (see notes).

Notes:

a) Pre-existing cardiovascular disease defined as having experienced a prior cardiovascular disease event (ie. myocardial infarction, angina, percutaneous coronary intervention, coronary artery bypass grafting, ischaemic stroke, transient ischaemic attack), or having peripheral vascular disease or congestive heart failure.

b) High cardiovascular risk defined as familial hypercholesterolaemia or an absolute 5-year cardiovascular disease risk of 15% or greater according to a validated cardiovascular risk assessment calculator.

11.5. The Committee considered the following when making its recommendation:

11.5.1. the high health need of individuals with a BMI ≥50 kg/$m^2$, including the physical impacts of higher weight and increased comorbidities including type two diabetes and sleep apnoea.

11.5.2. the effectiveness of liraglutide in reducing weight.

11.6. The Committee noted it would welcome applications to Pharmac for GLP-1 inhibitors, for weight management for groups with unmet high health needs, supported by clinical trial and/or other applicable evidence.

## Discussion

*Māori impact*

11.7. The Committee discussed the impact of funding liraglutide for weight management of individuals with a BMI 55kg/$m^2$and over, with high cardiovascular risk, without type two diabetes mellitus (T2DM), unable to access bariatric surgery; and Māori and/or Pacific people with BMI 50kg/$m^2$and over, with high cardiovascular risk, without T2DM on Māori health areas of focus and Māori health outcomes.

11.8. The Committee noted Mack et al. Ethn Health. 2023;28:562-85 had recommended the urgent implementation of Māori and Pacific-led, culturally tailored weight loss programmes that promote holistic, small and sustainable lifestyle changes delivered in socially appropriate contexts.

11.9. The Committee reiterated its previous considerations that Māori were inequitably burdened by cardiovascular disease, type 2 diabetes, and the need for osteoarthritis-associated large joint replacements, conditions for which obesity is a risk factor. The Committee considered that Māori are also more likely than non-Māori to live in areas of higher socioeconomic deprivation, increasing these inequities and potentially increasing inequities of access to treatment.

*Populations with high health needs*

11.10. The Committee discussed the health need(s) of liraglutide among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs. The Committee discussed the impact of funding liraglutide and noted its previous considerations that:

11.10.1. certain groups experienced elevated rates of obesity including Māori, Pacific peoples and South Asian ethnicities, disabled people, those experiencing socioeconomic deprivation, and those residing in urban areas

11.10.2. Pacific women have a higher prevalence of class three obesity (BMI >40 kg/m$^2$) than any other ethnicity and gender.

*Background*

11.11. The Committee noted the application for liraglutide for weight management of individuals with a BMI 55kg/m$^2$ and over, with high cardiovascular risk, without type two diabetes mellitus (T2DM), unable to access bariatric surgery; and for Māori and/or Pacific people with BMI 50kg/m$^2$and over, with high cardiovascular risk, without T2DM was reviewed by both the Committee in November 2022, and by the Diabetes Advisory Committee in April 2023. Both Committees deferred making recommendations, pending better identification of appropriate population groups with high unmet health needs.

11.12. The Committee noted that:

11.12.1. both it (PTAC) and the Diabetes Advisory Committee (April 2023) had considered the proposed group for funding was likely not the only one that would benefit, and that evidence was unavailable to directly inform the restriction to those with a BMI ≥55 kg/m$^2$ or a BMI ≥50 kg/m$^2$ for Māori or Pacific peoples, or to age-restrict to people aged 35 to 44 years

11.12.2. internationally, the funding of the GLP-1 agonist treatments for weight management has been targeted to populations with a BMI of ≥30 kg/m$^2$ or ≥35kg/m$^2$ with at least one weight-related comorbidity (for example hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes, or type 2 diabetes mellitus) or non-diabetic hyperglycaemia with a high risk of cardiovascular disease

11.12.3. the Diabetes Advisory Committee had suggested groups that might have the greatest potential to experience a treatment benefit from liraglutide include people with pre-diabetes, at high incipient risk of cardiovascular disease, at risk of other obesity-related complications, or unable to access surgical intervention and/or imaging because of the extent of their obesity

11.12.4. the Endocrinology Advisory Committee in August 2022 had noted the unmet health need of children with Prader-Willi syndrome and that inadequately managed Prader-Willi syndrome is associated with obesity

11.12.5. other groups that could also be considered included:

- people with conditions that result in appreciable secondary weight gain such as polycystic ovarian syndrome and Cushing syndrome due to pituitary adenoma
- children with Bardet-Biedl syndrome, pseudohypoparathyroidism, monogenic obesity, or hypothalamic obesity.

11.13. The Committee reiterated its view that there is an unmet health need for weight management treatments, but that it is challenging to identify specific populations that would experience the most health benefit. The adverse event profile of this class of drugs has not been well delineated, with limited long term follow up data for a number of agents. In addition, across GLP-1 agonists the trial designs vary on the population included, as well as primary and secondary endpoints, and trial study populations did not necessarily relate to those in Aotearoa New Zealand particularly Māori and Pacific peoples.

*Health need*

11.14. The Committee noted that no additional evidence was provided by the supplier since the application was reviewed in April 2023.

11.15. The Committee noted that in the UK liraglutide is recommended for funding for individuals BMI ≥35 kg/m$^2$ (or at least 32.5 kg/m$^2$ for members of minority ethnic groups known to be at equivalent risk of the consequences of obesity at a lower BMI than the NZ European population), as well as having a high risk of type two diabetes or cardiovascular disease.

11.16. The Committee noted a systematic review that evaluated interventions for prevention and management of obesity amongst Māori and Pacific adults and identified enablers and barriers to their uptake (Mack et al. Ethn Health. 2023;28:562-85). The study reported that interventions that result in modest weight loss or no weight gain over several years may have a positive outcome in delaying progression to diabetes, or improving glycaemic control in people with diabetes. The authors recommended urgent implementation of Māori and Pacific-led, culturally tailored weight loss programmes that promote holistic, small and sustainable lifestyle changes delivered in socially appropriate contexts.

11.17. The Committee considered that in general practice, the availability of both health improvement practitioners and health coaches were enablers of uptake of weight-management interventions, whilst barriers to weight management included limited practitioner time, lack of care continuity, obesogenic environments, and cost.

11.18. The Committee noted the Clinical Guidelines for Weight Management in New Zealand Adults that recommended that some other weight loss medications may be useful in producing initial weight loss and preventing weight regain in longer term management. These were recommended in individuals if the person had a BMI greater than 30 kg/m$^2$ and lifestyle changes had not produced significant benefit after at least six months.

*Health benefit*

11.19. The Committee noted the mechanism of action of liraglutide is through appetite regulation, as well as slowing gastric emptying, increasing satiety and regulating the release of insulin and glucagon secretion.

11.20. The Committee noted that it had previously reviewed evidence of health benefit, including the SCALE Obesity and Prediabetes trial reporting liraglutide treatment resulting in weight reduction in the population studied (le Roux et al. Lancet. 2017;389:1399-1409). The trial's reliability was limited by high losses to follow-up, with 50% of participants not completing the study up to week 160 despite the study timeframes being 205 weeks in total. The Committee reiterated its consideration that individuals in both trial arms received concomitant lifestyle management and dietary advice throughout the trial that resulted in a decreased caloric diet and increased physical activity in both arms. The Committee considered these services may not be available to all individuals in New Zealand and therefore might not be reflective of clinical practice in the New Zealand population.

11.21. The Committee noted that SCALE reported that the proportional weight loss effect (relative to baseline weight) was lower when individuals started with a BMI that was higher.

11.22. The Committee noted the Kitahara et al. PLoS Med. 2014;11:e100167 analysis, which reported the association between a BMI of 40-59 kg/m$^2$ (class three obesity) and mortality. The Committee noted the authors reported that class three obesity is associated with increased mortality with most deaths being due to cancer, heart disease, and diabetes. The Committee considered this increased mortality would affect the populations under consideration.

11.23. The Committee noted Bhaskaran et al. Lancet Diabetes Endocrinol. 2018;6:944-53, a population based cohort of 3.6 million individuals in the UK. The Committee noted the study reported that BMI had a J-shaped association with mortality, certain cancers, and a range of other cardiometabolic complications. The Committee noted that this study did not report how the risk of mortality and other complications changes for BMIs higher than 50kg/m$^2$, although it was reasonable to assume that the risk of such complications continued to rise steeply. The Committee considered that a reduction in BMI among those with a BMI greater than 50kg/m$^2$ would likely result in a risk of mortality reduction.

11.24. The Committee noted Kritchevsky et al. PLoS One. 2015;10:e0121993, an analysis of 15 randomised controlled trials comparing weight loss and all mortality between individuals in weight loss or non-weight loss arms. The weight loss groups experienced a 15% lower all-cause mortality risk (RR = 0.85; 95% CI: 0.73-1.00).

11.25. The Committee noted the Bartelt et al. Epic Research. 2024 observational reporting that more than 50% of individuals were able to maintain the weight loss achieved while on semaglutide or liraglutide even a year after discontinuing the medication. However, Members considered reporting was limited by being provided in a non-Medline indexed setting without clear peer-review and with insufficient information on the dataset's source population or the report's methods, insufficient follow-up time (beyond the 12 months observed, as with other studies in weight loss), and sparse results with no stratification. Members further noted that a proportion of individuals in the dataset who stopped taking either medication experienced weight regain, with 18.7% of liraglutide users and 17.7% of semaglutide users regaining all the weight they had lost or more.

11.26. The Committee considered that appetite was not the sole driver of excess or imbalanced eating and drinking behaviour. The Committee noted that across many communities, practices around the consumption of food were linked to cultural belonging and value systems including manaakitanga.

11.27. The Committee noted that there was a lack of long-term safety data for the use of liraglutide in weight management.

11.28. The Committee considered other GLP-1 agonists may have a greater effect on weight loss compared to liraglutide. The Committee welcomed applications for other pharmaceuticals in the management of weight.

11.29. Overall, the Committee considered that community-based programmes would be needed, in addition to liraglutide. In addition, cultural tailoring to delivery would be necessary. The Committee considered this would require a coordinated health system response.

*Suitability*

11.30. The Committee noted its previous considerations that the daily injection formulation of liraglutide was less desirable than weekly injectable GLP-1 agonists.

*Cost and savings*

11.31. The Committee considered that there was limited capacity within the publicly funded health system to deliver wrap-around weight management care, that this was crucial to realising the full benefits of GLP-1 agonist treatment, and that there was little trial evidence for the impact of liraglutide associated weight loss in the absence of these measures. The Committee considered that funding liraglutide may increase demand for these services, and if there was not sufficient investment by health entities to upscale these services, this demand would disproportionately fall on and impact primary care.

11.32. The Committee considered the weight loss and health benefits of liraglutide were inferior to bariatric surgery, which provided more durable results, with the cost of liraglutide higher over the lifetime of the individual. The Committee noted there was limited access to bariatric surgery, and individuals with a BMI greater than 45 were required to reduce their weight before being able to access this service.

11.33. The Committee considered that GLP-1 agonist treatment would generally be long-term, and funding such treatments would result in ongoing pharmaceutical costs. The Committee considered that these costs should be weighed against savings to the wider health sector from reduced risk of obesity-related complications, as well as the additional costs required to scale-up weight management services.

*General*

11.34. The Committee noted that the application submitted to Pharmac and considered again at this meeting comprised a small subset of potential groups who would potentially benefit

from liraglutide, or GLP-1 agonists in general, for weight management. The Committee also noted that in assigning a positive recommendation to list liraglutide in this setting with a low priority, that the application was not necessarily for groups with the highest need and/or potential to benefit, and that any future recommendations for applications for other groups may eventually receive different priorities from itself (PTAC) and/or the Pharmac Endocrine and/or Diabetes Specialist Advisory Committees.

11.35. The Committee did not provide a summative view on which groups of people and/or clinical circumstances might have the greatest need and/or greatest potential for treatment benefit.

11.36. The Committee considered this wider issue would benefit from a holistic approach that included addressing primary care issues, where the majority of people with obesity are seen in that setting.

11.37. The Committee stated it would welcome applications to Pharmac for liraglutide or alternative treatments for weight management for groups with unmet high health needs supported by clinical trial and/or other applicable evidence.

*Summary for assessment*

11.38. The Committee considered that elements of the PICO (population, intervention, comparator, outcomes) for this application are unclear/uncertain at this time. The PICO may be developed based on additional clinical advice or information received by Pharmac.

## 12. Benralizumab - widening access to adult patients diagnosed with eosinophilic granulomatosis with polyangiitis (EGPA)

### Application

12.1. The Committee reviewed the supplier application from AstraZeneca for the use of benralizumab (Fasenra pen) for the treatment of eosinophilic granulomatosis with polyangiitis (EGPA). The Committee noted that Pharmac staff sought advice regarding proposals to widen access to benralizumab (and mepolizumab) for:

12.1.1. first-line (1L) biologic use of benralizumab for the population with relapsed or refractory EGPA who are eligible for mepolizumab

12.1.2. second-line (2L) biologic use of either mepolizumab or benralizumab for those people with relapsed or refractory EGPA who experience intolerance to, or who receive sufficient benefit from, either mepolizumab or benralizumab as a first-line biologic.

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

### Recommendation

12.3. The Committee **recommended** that access to benralizumab be widened for the first-line (1L) treatment of EGPA with a **high priority**, subject to the following Special Authority criteria (identical to that currently in place for mepolizumab):

> Initiation – eosinophilic granulomatosis with polyangiitis
> Applications only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months.
> All of the following:
> 1. The patient has eosinophilic granulomatosis with polyangiitis; and
> 2. The patient has trialled and not received adequate benefit from at least one of the following for at least three months (unless contraindicated to all): azathioprine, cyclophosphamide, leflunomide, methotrexate, mycophenolate, or rituximab; and
> 3. Either:
>  3.1. The patient has trialled prednisone for a minimum of three months and is unable to maintain disease control at doses below 7.5 mg per day; or
>  3.2. Corticosteroids are contraindicated.

Continuation – eosinophilic granulomatosis with polyangiitis
Applications only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months.
1. Patient has no evidence of clinical disease progression.

12.3.1. In making this recommendation, the Committee considered:

12.3.2. the high health needs of people with EGPA whose survival is further reduced when there is a greater extent of organ involvement

12.3.3. there is high quality phase III clinical trial evidence of non-inferior remission and a similar reduction in oral corticosteroid use with benralizumab compared with mepolizumab for EGPA

12.3.4. that people with EGPA may benefit from having another funded 1L biologic option with a different mechanism of action.

12.4. The Committee **recommended** that access to benralizumab and mepolizumab be widened for the second-line (2L) treatment of EGPA with a **medium priority**, subject to the following Special Authority criteria (additions shown in **bold**):

[MEPOLIZUMAB/BENRALIZUMAB]
Initiation – eosinophilic granulomatosis with polyangiitis
Applications only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months.
All of the following:
1. The patient has eosinophilic granulomatosis with polyangiitis; and
2. The patient has trialled and not received adequate benefit from at least one of the following for at least three months (unless contraindicated to all): azathioprine, cyclophosphamide, leflunomide, methotrexate, mycophenolate, or rituximab; and
3. Either:
    3.1. The patient has trialled prednisone for a minimum of three months and is unable to maintain disease control at doses below 7.5 mg per day; or
    3.2. Corticosteroids are contraindicated**; and**
4. **Either:**
    **4.1 Patient has not previously received an anti-IL5 biological therapy for their severe eosinophilic asthma; or**
    **4.2 Both:**
        **4.2.1 Disease was refractory or the patient experienced intolerance to previous anti-IL5 biological therapy; and**
        **4.2.2 Patient was not eligible to continue treatment with previous anti-IL5 biological therapy and discontinued that treatment.**

Continuation – eosinophilic granulomatosis with polyangiitis
Applications only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months.
1. Patient has no evidence of clinical disease progression.

12.5. In making this recommendation, the Committee considered

12.5.1. the high health needs of people with EGPA, of whom a substantial proportion will not have an adequate clinical response or any disease response to mepolizumab or other funded 1L treatments, and thus have an unmet health need for a 2L biologic treatment

12.5.2. that there was low and very low-quality evidence of a health benefit from benralizumab and mepolizumab, respectively, in the 2L setting although the magnitude of benefit is less than that seen with 1L use. This was unable to be quantified due to limitations of the evidence base

12.5.3. that benralizumab and mepolizumab would be expected to provide similar health benefits in the 2L setting.

12.6. The Committee considered that Pharmac staff should seek advice from the Respiratory Advisory Committee regarding: the proposed 2L funding criteria (including definitions of *refractory* and *intolerant*); whether benralizumab or mepolizumab would be the preferred

1L option for people newly initiating a biologic for EGPA, and which mepolizumab dose would be used in practice.

**Discussion**

*Māori impact*

12.7. The Committee discussed the impact of widening access to benralizumab and mepolizumab for the treatment of EGPA on Māori health areas of focus | Hauora Arotahi and Māori health outcomes. EGPA is not a Māori health area of focus. The Committee considered the comments made by the Respiratory Advisory Committee in April 2022 remained relevant.

*Populations with high health needs*

12.8. The Committee discussed the health need(s) of people with EGPA among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs. The Committee considered the comments made by the Respiratory Advisory Committee in April 2022 remained relevant, and Members had no additional comments.

*Background*

12.9. The Committee noted that benralizumab is funded for the treatment of severe eosinophilic asthma (SEA), subject to funding criteria, and Pharmac has considered proposals to widen access to benralizumab (and mepolizumab) for SEA by changing or removing criteria for the Asthma Control Test (ACT) and eosinophil count. The Committee noted that in November 2024, PTAC considered a proposal to widen access to both benralizumab and mepolizumab for 2L biologic treatment of SEA.

12.10. The Committee noted that mepolizumab (100 mg prefilled pen) for EGPA was considered and recommended for funding with a high priority by the Respiratory Advisory Committee in April 2022; subsequently access was widened in May 2024, subject to funding criteria.

*Health need*

12.11. The Committee noted that EGPA is a multisystem autoimmune disorder with characteristics of both severe eosinophilic asthma (SEA) and vasculitis as described by the Respiratory Advisory Committee in 2022. The Committee was made aware of the Five Factor Score which can be used to estimate five-year survival in EGPA; this system assigns one point for disease involvement in specific organs (kidneys, gastrointestinal tract, heart or central nervous system) with scores of zero, one and two or more corresponding to five-year survival rates of 88.1%, 74.1% and 54.1%, respectively (Moiseev and Novikov. Ann Rheum Dis. 2014;73:e12). The Committee noted that EGPA is associated with significant reductions in health-related quality of life (QoL) and frequent interactions with the healthcare system.

12.12. The Committee was made aware of a proposed treatment algorithm for relapsing EGPA, which indicates that people with non-severe EGPA might be appropriately treated with corticosteroids alone or with mepolizumab alongside optimisation of inhaled therapies, whilst those with severe systemic relapse might require treatment with high-dose oral corticosteroids plus cyclophosphamide or rituximab (Emmi et al. Nat Rev Rheumatol. 2023;19:378-93). The Committee noted that the key phase III randomised clinical trial investigating mepolizumab versus placebo for EGPA reported that, of those receiving mepolizumab, about 40% of participants experienced remission and about 50% remained without relapse at 52 weeks (Wechsler et al. N Engl J Med. 2017;376:1921-32).

12.13. Members considered that in the pivotal clinical trial for mepolizumab, those receiving a suboptimal response would have been managed with additional oral corticosteroids (OCS) or other treatments, and currently a large proportion of people receiving mepolizumab 1L for EGPA would continue it with and despite a suboptimal response. The Committee considered that the substantial proportion of people with EGPA without a response to

mepolizumab 1L or other funded treatments thus have an unmet health need for a 2L treatment, and some might benefit from the availability of a 1L treatment with a different mechanism of action (ie benralizumab).

*Health benefit*

12.14. The Committee noted that benralizumab (Fasenra pen) is a humanised monoclonal antibody targeting the IL-5 receptor. The Committee noted that benralizumab is Medsafe registered for the treatment of adult patients with EGPA and as add-on therapy in patients aged 12 years and over with SEA (blood eosinophil count ≥300 cells/μL or ≥150 cells/μL if on oral corticosteroid treatment). The Committee noted that the recommended dose in EGPA is 30 mg every four weeks, which is higher than the maintenance dose of 30 mg every eight weeks for SEA, and that it is administered as a subcutaneous (SC) injection.

12.15. The Committee noted that the supplier proposed widening access to benralizumab to include people with relapsed or refractory EGPA (matching the criteria for mepolizumab), to give treating clinicians an additional choice of 1L treatment, and that the application included evidence for consideration of 2L biologic use of benralizumab for EGPA.

First-line benralizumab

12.16. The Committee noted evidence from the MANDARA trial, a multicentre, double-blind, phase III, randomised (1:1), active-controlled noninferiority trial with an open-label 1 year extension (Wechsler et al. N Engl J Med. 2024;390:911-21). The study included 140 adults with relapsing or refractory EGPA who were receiving standard care (oral corticosteroid +/- stable immunosuppressive therapy). Participants received 1L biologic treatment with either benralizumab (30 mg) or mepolizumab (300 mg) subcutaneously every four weeks for 52 weeks.

12.16.1. The Committee noted that participants were of average age for the disease and the study included relapsing, refractory and relapsing-refractory disease types. The Committee noted that only 10% were anti-neutrophil cytoplasmic antibody (ANCA) positive at screening, and considered this small proportion was an effect of corticosteroid usage leading to ANCA-negative status. However, the Committee noted that the study population had a high mean blood eosinophil count, indicating that for many their disease remained uncontrolled. Members considered there were likely some differences in participant characteristics in the MANDARA trial compared with those in the pivotal trial of mepolizumab in EGPA (Wechsler et al. 2017), and that this might have contributed to a difference in the magnitude of efficacy with mepolizumab between the two trials, alongside the seven years' gap between publications suggesting possible confounding from changes in standard of care and diagnosis.

12.16.2. The Committee noted that the mean Birmingham Vasculitis Activity Score (BVAS) score was two, with half of participants having a score of greater than zero indicating some disease activity. However, the Committee noted the vasculitis damage index reflected the occurrence of vascular damage, which members considered reflected active disease and was likely more clinically relevant than blood eosinophil counts and the extent of eosinophilic asthma.

12.16.3. The Committee noted there was no difference in the primary endpoint between groups, with an adjusted percentage of patients with remission at 36 and 48 weeks (prespecified noninferiority margin, –25 percentage points) of 59% with benralizumab versus 56% with mepolizumab (difference, 3 percentage points; 95% confidence interval [CI], –13 to 18; *P*=0.73 for superiority). Members considered that it was clear by 12 months which participants had refractory disease or had relapsed.

12.16.4. The Committee noted that ≥70% of participants in each group had a reduction in oral corticosteroid use to ≤4 mg per day. The Committee considered these individuals were therefore in remission and the reported between-group difference

in complete discontinuation of oral corticosteroids (41% benralizumab vs 26% mepolizumab) was not clinically significant.

12.17. Members considered that neutralising anti-drug antibodies occur more commonly with benralizumab than mepolizumab, and that this might be seen as waning efficacy if benralizumab were funded and increasingly used first-line for EGPA.

Second-line benralizumab or mepolizumab

12.18. The Committee noted a multicentre, retrospective observational study of 68 people with EGPA who had previously received mepolizumab for a median of 10.2 months (6.1 to 25.2 months) (Cottu et al. Ann Rheum Dis. 2023;82:1580-6). Benralizumab was used off-label 2L based on asthma dosing (30 mg every four weeks three times, then 30 mg every eight weeks, used in 63 out of 66 participants [96%]) and was commenced for uncontrolled asthma, uncontrolled ear nose and throat (ENT) manifestations or persistent corticosteroid use.

12.18.1. The Committee noted that 31 people had previously received mepolizumab and had less atopy and more tobacco use than those who had no previous mepolizumab; the Committee therefore considered the groups were not particularly well matched. The Committee noted that the primary endpoint was the rate of complete response, defined as no disease activity (BVAS=0) and a prednisone dose ≤4 mg/day. Partial response was defined as no disease activity and a prednisone dose ≥4 mg/day, members noting the ambiguity with the 4mg daily dose being in both measures.

12.18.2. The Committee noted that the greatest proportion of complete responses were in people who had not received prior mepolizumab (P=0.026). However, Members considered that selection bias may have resulted in the group enrolled experiencing a very high total response from 1L benralizumab, and thus some caution was required when interpreting the outcomes of this study.

12.18.3. The Committee noted that a greater proportion of those without prior mepolizumab were able to withdraw from corticosteroids compared with those who had prior mepolizumab (P<0.01). The Committee noted that a greater proportion of those who experienced primary failure to receive remission from benralizumab had prior mepolizumab (P=0.034). Overall, the Committee considered that while those receiving 1L treatment received the most benefit, those who received 2L treatment still received some benefit.

12.18.4. The Committee noted that the proportions of patients with at least one asthma exacerbation at 12 and 24 months, respectively, were ~35% and ~42% with previous mepolizumab compared with ~15% and ~18% without previous mepolizumab (P<0.05).

12.18.5. The Committee noted that 20% of those who received previous mepolizumab withdrew from benralizumab due to insufficient efficacy (vasculitis flares, uncontrolled asthma and/or uncontrolled ENT manifestations), and considered it reasonable to assume this rate of drop-off over time if funded in the 2L setting.

12.19. The Committee was made aware of a single case report of an individual with EGPA who received benralizumab 1L until eosinophil count re-elevation, then switched to mepolizumab 2L which led to apparent improvement and remission (Yukishima et al. Mod Rheumatol Case Rep. 2025:rxaf008).

General

12.20. The Committee noted evidence of mepolizumab being used for the treatment of EGPA at either a 100 mg dose (as indicated for the treatment of SEA) or a higher 300 mg dose (intended for the treatment of EGPA) from a multicentre observational study of sequential rituximab and mepolizumab in EGPA (Bettiol et al. Ann Rheum Dis. 2022;81:1769-72). The Committee noted that most participants (83%) participants received the lower dose, as they were treated for SEA rather than EGPA, and they experienced no adverse effects

associated with this dosing, with similar BVAS scores and prednisone dosing between the dose groups. The Committee noted that there was no association with higher incidence of adverse events in those receiving the higher dose, and that the higher dose was not associated statistically significantly with either a greater proportion of complete responses or any difference in OCS sparing. However, Members expressed concerns about the quality of this retrospective study (and therefore uncertainty in its outcomes), due to BVAS scoring being performed retrospectively despite the low likelihood of having sufficient clinical notes to do this accurately.

12.21. The Committee noted the following additional evidence:

- Hellmich et al. Ann Rheum Dis. 2024;83(Suppl 1):186-7
- Weschler et al. Am J Respir Crit Care Med. 2024;209:A5364
- Maynard-Paquette et al. Thorax. 2323;78(Suppl 1):A49-50
- Alam et al. Thorax. 2022;77(Suppl 1):A195
- Desaintjean et al. Eur Respir J. 2022;60(Suppl 66)
- Nanzer et al. Thorax. 2021;76(Suppl 1):A140-1
- Caminati et al. J Clin Med. 2023;12:1836
- Mattioli et al. Ann Rheum Dis. 2024;83(Suppl 1):390-1
- Hellmich et al. Ann Rheum Dis. 2024;83:30-47
- Guntur et al. J Allergy Clin Immunol Pract. 2021;9:1186-93.e1
- Condreay et al. Rheumatol Int. 2020;40:1301-7.

12.22. The Committee was made aware of the following evidence for 1L mepolizumab in EGPA:

12.22.1. An observational study based on US claims data, which examined treatment patterns and health outcomes including EGPA-related hospitalisations (Mathur et al. Ann Allergy Asthma Immunol. 2025;134:341-350.e2). Members considered that the reported reductions in hospitalisations associated with mepolizumab would likely also be seen with benralizumab in this setting for EGPA.

12.22.2. A conference abstract reporting an observational study of improvement in patient-reported outcomes (PROs) associated with mepolizumab in EGPA (Delvino et al. Ann Rheum Dis. 2024;83;388-9). Members considered a similar apparent improvement in PROs would be plausible with benralizumab.

12.22.3. A propensity score-matched retrospective cohort study reporting five-year survival associated with mepolizumab being superior to non-mepolizumab in EGPA (Shiomi et al. Front Immunol. 2024:15:1457202). Members considered that although this study was limited by its design and sample size, this suggested a possible survival improvement with mepolizumab which similarly could be possible with benralizumab.

12.23. Overall, the Committee considered that despite limitations of the evidence, it was plausible that benralizumab provided clinical benefits when used either 1L or 2L for EGPA, although the greatest benefit would be provided in the 1L setting. The Committee considered the evidence base for 2L mepolizumab following benralizumab was minimal and of very low quality, but that it was plausible that 2L mepolizumab could provide similar benefits to 2L benralizumab for EGPA.

*Suitability*

12.24. The Committee noted that while four-weekly dosing of benralizumab is the same as mepolizumab for EGPA, the number of injections differs between these biologics: benralizumab is administered as a single SC injection (30 mg), while 300 mg of mepolizumab is given as three successive 100 mg SC injections. The Committee considered that both mepolizumab doses (100 mg and 300 mg) appeared appropriate for

use in practice for EGPA, based on the Bettiol et al. (2022) study and the significant overlap with SEA in the EGPA population. Members considered there were no patient preference data to inform this, and therefore that it was unclear whether the number of injections would be a strong factor in deciding which biologic would be preferred for EGPA, if both were funded. The Committee considered that Pharmac could seek advice from the Respiratory Advisory Committee regarding this.

*Cost and savings*

12.25. The Committee considered that if benralizumab was funded for EGPA (1L and 2L) and mepolizumab was funded 2L, a substantial and increasing proportion of people receiving 1L treatment would be likely to discontinue the 1L biologic and switch to 2L treatment, given that ~40-50% will not receive remission with a 1L biologic. Members considered that this subgroup could be in the range of 20-30% based on the evidence (~40-50% not receiving remission, ~20% discontinuing). The Committee considered it reasonable to assume similar rates of treatment persistence on benralizumab and mepolizumab in the first-line setting.

12.26. The Committee considered that ~20% of individuals with EGPA would stop a 2L biologic treatment upon a major relapse and ~80% would likely continue receiving a 2L biologic even if they experienced a minor relapse (ie not requiring hospitalisation for symptom management).

12.27. The Committee considered that, despite some study participants receiving treatment for SEA rather than EGPA, it was not appropriate to apply data from SEA to EGPA. The Committee considered that this is because: EGPA involves vasculitis while SEA does not; individuals may receive different dosing and treatments depending on the intent of treatment (ie for SEA or EGPA); and there is a substantial difference in health system resource use associated with the two conditions, with EGPA having a greater impact.

12.28. The Committee considered that the availability of two biologics for EGPA might lead to a reduction in health system costs from better disease control (ie fewer hospitalisations and less emergency department visits).

*Funding criteria*

12.29. The Committee considered the proposed funding criteria for benralizumab for the 1L treatment of EGPA, and for both benralizumab and mepolizumab for the 2L treatment of EGPA, to be appropriate and that re-assessment at 12 months was suitable. However, the Committee considered that Pharmac could seek advice from the Respiratory Advisory Committee around this.

*Summary for assessment*

12.30. The Committee considered that the below summarises its interpretation of the most appropriate PICO table (population, intervention, comparator, outcomes) information for benralizumab if it were to be funded in New Zealand for 1L treatment of EGPA, and benralizumab and mepolizumab if they were funded for 2L treatment of EGPA. This PICO table captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO table is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO table may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

| | | |
|---|---|---|
| Population | **First-line:** People with relapsed or refractory EGPA who meet the current criteria for mepolizumab including:<br>• Unable to reduce prednisone dose below 7.5 mg daily or oral corticosteroids (OCS) cannot be tolerated.<br>• Trialled and not received adequate benefit from at least one of the following: cyclophosphamide, azathioprine, mycophenolate, methotrexate, leflunomide, or rituximab | **Second line:** People with EGPA who have received either benralizumab or mepolizumab and have discontinued due to waning efficacy or insufficient/suboptimal benefit. |
| Intervention | Benralizumab 30 mg every four weeks as a first-line (1L) biologic | Benralizumab 30 mg every four weeks **or mepolizumab** 300 mg every four weeks as a second-line (2L) biologic |
| Comparator(s) | Mepolizumab at a maximum dose of 300mg every four weeks | 1) Best supportive care with OCS +/- rituximab or<br>2) Continued suboptimal benefit from mepolizumab for a small proportion of people. |
| Outcome(s) | The MANDARA trial of benralizumab compared to mepolizumab in EGPA indicates the following:<br>• Non inferior remission compared with mepolizumab<br>• Similar reduction in OCS use compared with mepolizumab | **Uncertainty in:**<br>• Reduced magnitude of benefit from a second-line biologic (vs its use in 1L), including induction of remission (Birmingham Vasculitis Activity Score (BVAS) score of 0 and ≤4 mg of prednisone per day), freedom from exacerbations, reduction in OCS use and improvement in survival.<br>• The extent to which second-line biologics would provide incremental benefit, beyond continuing with a first-line biologic with suboptimal benefit. |
| Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data. | | |