Record of the Cancer Treatments Advisory Committee Meeting held on Friday, 28 October 2022

This meeting was held virtually and in person

Cancer Treatments Advisory Committee records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) Specialist Advisory Committees 2021.

Note that this document is not necessarily a complete record of the Cancer Treatments Advisory Committee meeting; only the relevant portions of the meeting record relating to Cancer Treatments Advisory Committee discussions about an application or Pharmac staff proposal that contain a recommendation are generally published.

The Cancer Treatments Advisory Committee may:

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

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

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

Pharmac Advisory Committees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Advisory Committee meeting will be reviewed by PTAC at an upcoming meeting.

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

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

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1. Attendance

Present	Apologies
Marius Rademaker (Chair, parts of)	Lochie Teague
Allanah Kilfoyle (parts of)	
Anne O'Donnell	
Christopher Frampton	
Scott Babington	
Oliver Brake	
Peter Ganly	
Richard Isaacs	
Vidya Mathavan	
Stephen Munn (Chair, for parts of)	
Matthew Strother	
Michelle Wilson	

2. The role of Specialist Advisory Committees and records of meetings

2.1. This meeting record of the Cancer Treatments Advisory Committee is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and Specialist Advisory Committees 2021, available on the Pharmac website at https://pharmac.govt.nz/assets/2021-Specialist-Advisory-Committee-Terms-of-Reference.pdf. The Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of Specialist Advisory Committees and PTAC.

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

2.3. The Cancer Treatments Advisory Committee is a Specialist Advisory Committee of Pharmac. The Cancer Treatments Advisory Committee and PTAC and other Specialist Advisory Committees have complementary roles, expertise, experience, and perspectives. The Cancer Treatments Advisory Committee and other Specialist Advisory Committees may therefore, at times, make recommendations for treatments for malignant disease that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for treatments for malignant disease that differ from the Cancer Treatments Advisory Committee's, or Specialist Advisory Committees may make recommendations that differ from other Specialist Advisory Committees'.

2.4. Pharmac considers the recommendations provided by both the Cancer Treatments Advisory Committee and PTAC and any other relevant Specialist Advisory Committees when assessing applications for treatments for malignant disease.

3. Record of PTAC meetings held 19 & 20 May 2022, and 18 & 19 August 2022

The Advisory Committee reviewed the record of the PTAC meeting held on 19 & 20 May 2022, at which PTAC reviewed the record of CaTSoP's meeting held on 4 and 5 November 2021.

3.1. The Advisory Committee reviewed the record of the PTAC meeting held on 18 & 19 August 2022, at which PTAC reviewed the record of CTAC's meeting held on 8 April 2022.

3.2. The Advisory Committee had no comments regarding the record of the PTAC meetings.

4. Record of CTAC meeting held Friday, April 8, 2022

4.1. The Advisory Committee reviewed the record of the CTAC meeting held on 8 April 2022 and agreed that the record be accepted.

5. Correspondence – Multiple Myeloma

Discussion

5.1. The Committee considered that it would be beneficial for correspondence of this kind to be reviewed by the Consumer Advisory Committee.

5.2. The Committee noted that there is no new content compared to what has been previously considered. The Committee noted that the correspondence identified a clear unmet need for better treatment in the relapsed /refractory setting. The Committee noted that this was in alignment with the preference communicated by the NZMIG and reflected by CTAC at its previous meetings (April 2021, July 2021, November 2021). The Committee noted that the highest priority communicated was for the funding of daratumumab, which was in line with its previous considerations and agreed with the sentiment of the correspondence received. The Committee noted that lenalidomide upfront for both transplant eligible and ineligible patients has been ranked as an option for investment, and that daratumumab, carfilzomib and pomalidomide for people who have received one prior line of therapy has been ranked as an option for investment.

5.3. The Committee considered that the lower toxicity of daratumumab would be preferential to current treatment options as well as other agents considered for funding previously (pomalidomide and carfilzomib). The Committee noted that it is available as a subcutaneous injection, which would also be expected to contribute to better quality of life and reduction in treatment burden for people receiving treatment.

5.4. The Committee noted the differences in access to treatments for multiple myeloma in New Zealand compared to Australia and acknowledged that this corresponds to a reduction in 5 year overall survival (OS) (45% in New Zealand and 51% in Australia) (Burden of Multiple Myeloma in New Zealand Report). The Committee noted that there is an increase in the frequency of multiple myeloma in Māori, that they have lower survival, worse outcomes and fewer autologous stem cell transplants. The Committee considered that with fewer Māori receiving an autologous SCT, the availability of more efficacious second line therapy would provide additional benefit for this group.

5.5. The Committee noted that it has previously reviewed the data from the CASTOR trial comparing daratumumab in combination with bortezomib and dexamethasone (DBorD), with bortezomib and dexamethasone. The Committee noted that this trial provides evidence that the addition of daratumumab to this doublet (BorD) improves response rates, progression free survival and overall survival, in particular in those patients who have received one prior line of therapy. The Committee noted a recent publication, in which the OS is reported after 6 years of follow up for the CASTOR trial. The Committee noted that a substantial improvement in OS is presented for the intention to treat population (Hazard Ratio, HR, 0.74 95% CI: 0.59-0.92), with the most profound benefit seen in those who have received one prior line of therapy (HR, 0.56 95% CI: 0.39-0.80) (Sonneveld et al. HemaSphere. 2022; 6:12). The Committee noted that this data had been previously provided in confidence by the supplier to the

Committee. The Committee considered that the clear benefit of treatment in this patient population has been described well in previous meetings.

5.6. The Committee considered that for those too frail to receive doublet or triplet therapy, there is evidence of single agent daratumumab efficacy. The efficacy of single agent would be expected to be less than doublet or triplet therapy. The Committee considered that if a patient is too frail to receive doublet or triplet therapy, treatment with other options such as daratumumab may not be appropriate. The Committee considered that the access criteria for daratumumab monotherapy would need to be considered separately to the access criteria for daratumumab in conjunction with a doublet or triplet therapy.

5.7. The Committee noted that it had not previously reviewed daratumumab in combination with lenalidomide and dexamethasone (DLenD). The Committee noted that the POLLUX trial describes an OS benefit for DLenD compared to the combination of lenalidomide and dexamethasone (HR 0.73 95% CI: 0.58-0.91) (Dimopoulos et al. HemaSphere. 2022; 6:13).

5.8. The Committee considered that the interpretation of which combination (DBorD or DLenD) is better is difficult, however, the Committee noted two meta analyses (hBotta et al. Blood Adv. 2017; 1(7):455-66; van Beurden-Tan et al. J Clin Oncol. 2017; 35(12):1312-1319), in which the authors concluded that DlenD is the most active combination for people with relapsed or refractory myeloma. The Committee however considered that the relative efficacy in any individual patient of DlenD and DBorD would largely depend on their prior exposure to therapy.

5.9. The Committee noted that people who receive transplantation receive lenalidomide maintenance and may therefore benefit more from DBorD than DLenD. Currently individuals in the non-transplant group may receive a benefit DLenD, but this would be predicated on the current lack of access to lenalidomide in the first line setting.

5.10. The Committee considered that the Special Authority criteria for daratumumab could be amended to enable its use in combination with lenalidomide. However, the preference would be to instead enable access to lenalidomide in the first line and the Committee considered that the availability of lenalidomide in this setting would reduce the need for this combination (DLenD). The Committee considered that if there were to be no restriction on the use of lenalidomide, then it would be preferential to enable access to daratumumab in combination with lenalidomide to enable clinician choice depending on prior exposure to therapy. The Committee noted the current funded access to lenalidomide and daratumumab in Australia, specifically that access to lenalidomide in the first line setting is less restrictive, but access to daratumumab after one prior line of therapy is restricted to in combination with bortezomib. The Committee considered that it would be appropriate to reflect this sequencing in New Zealand, which is in line with its previous recommendations and those proposals ranked as options for investment.

5.11. The Committee noted that the novel agents elotuzumab, ixazomib and selinexor do show promise. However, the Committee considered that there are clear priorities for funding, both within myeloma and across other haematological malignancies that should be prioritised over these novel agents.

5.12. The Committee acknowledged that the lack of access to daratumumab would likely reduce access to clinical trials for New Zealand patients, as certain clinical trials in this setting require prior exposure to daratumumab for entry. However, the

Committee considered that this limited access due to prior exposure to treatment is not something that is unique to people with multiple myeloma.

5.13. The Committee considered there to be a large positive impact on quality of life and survival that could be achieved with the funding of daratumumab and other agents for this population group. The Committee considered that the desire for therapies that prolong life and maintain quality of life described in the correspondence is shared by the Committee. The Committee considered that the funding of daratumumab would lead to significant improvements in myeloma therapy and outcomes.

6. Correspondence – Consultation feedback from Roche regarding pertuzumab for neoadjuvant treatment for HER2-positive, locally advanced, inflammatory or early-stage breast cancer

Recommendations

6.1. The Committee **recommended** that pertuzumab be listed with a **medium priority**, in the context of treatments for malignant disease, subject to the following Special Authority criteria:

> **Initial application – (breast cancer, neoadjuvant)** only from a relevant specialist or any other practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. The patient has breast cancer expressing HER2 IHC3+ or ISH+ (including FISH or other technology); and
> 2. The patient's condition is treatment naïve; and
> 3. Both:
> 3.1. The patient has locally advanced or inflammatory breast cancer; and
> 3.2. The patient has high risk early-stage breast cancer (either greater than 2 cm in diameter or node positive); and
> 4. Pertuzumab to be administered for a maximum of 4 cycles.

6.2. In making this recommendation the Committee considered the following:

- health need of people with HER-2 positive breast cancer, and
- breast cancer (including HER-2 positive) is an area of Māori health focus, and
- health benefit demonstrated by pathological complete response (pCR), and the health benefit associated with earlier treatment in many oncology indications, and
- reduced use of adjuvant therapy providing potential savings for the health system, and
- neoadjuvant treatment being more suitable than adjuvant treatment.

Discussion

6.3. The Committee noted that an application for pertuzumab for neoadjuvant treatment for HER2+ve, locally advanced, inflammatory or early-stage breast cancer was assessed by the Committee at their September 2018 meeting. The Committee had recommended this application be declined based on insufficient evidence and considered that any reconsideration would require additional evidence powered to detect a progression free survival (PFS) and overall survival (OS) benefit.

6.4. The Committee considered that the first trials (Gianni L, et al. Lancet Oncol. 2012;13(1):25-32 and Schneeweiss A, et al. Ann Oncol. 2013;24(9):2278-84) were in large heterogenous populations with high response rates but no clear survival benefit. The Committee considered that there was now supporting data that there was high pCR (pathological complete response) in certain phenotypes including HER2+ at 39-60%, which may correlate with a survival advantage.

6.5. The Committee noted a meta-analysis which reported that pCR was associated with improved event free survival and overall survival (OS) compared to non-pCR (Broglio et al. JAMA Oncol. 2016;2: 751-760). The Committee considered that the magnitudes of the associations between pCR and these final clinical endpoints were uncertain, limiting the ability to predict the absolute overall survival of pertuzumab in the neoadjuvant setting. The Committee noted however that in other jurisdictions, pCR was accepted as a surrogate marker for OS.

6.6. The Committee considered correspondence from the supplier (Roche) with further evidence to support its initial application. The Committee considered the 5-year follow up from the initial NeoSphere trial (Gianni L, et al. Lancet Oncol. 2016;17(6):791-800) and PEONY trial (Shao Z, et al. JAMA Oncol. 2020;6(3):e193692). The Committee considered the additional follow up from the NeoSphere trial had small participant numbers and noted the confidence interval of the relative PFS in treatment compared to non-treatment overlapped. The Committee considered that the assessment of the impact of pertuzumab on PFS was not strong based on this evidence. The Committee noted the PEONY study comparing those treated with docetaxel and trastuzumab alone with those treated with docetaxel, trastuzumab and pertuzumab in the neoadjuvant setting. The Committee noted that the trial reported a higher objective response rate (78% v 88%) and higher statistically significant pCR in the pertuzumab arm of the trial. The Committee noted that no OS or PFS data was reported in the paper. The Committee considered these outcomes were similar to the initial NeoSphere trial assessed in 2018. The Committee considered the low score from European Society for Medical Oncology (ESMO) clinical benefit scale, but noted the PEONY trial was not considered in this score.

6.7. The Committee noted seven other studies submitted by the supplier and considered they were not relevant to the application, as they contained pertuzumab in all trial arms and therefore did not provide evidence of the incremental benefit associated with pertuzumab. The Committee noted that generally, the earlier treatment was more beneficial in oncology indications. The Committee noted that an increasing proportion of trials of neoadjuvant therapies for HER2+ breast cancer contained pertuzumab as part of their backbone, and this reflected use of pertuzumab as standard of care in the neoadjuvant setting in other jurisdictions. The Committee considered given the use of neoadjuvant pertuzumab as standard of care in many other countries, that it was unlikely additional evidence would become available for this indication.

6.8. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for pertuzumab if it were to be funded in New Zealand for neoadjuvant treatment of HER2+ breast cancer. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with HER2 IHC3+ or ISH+ expressing, locally advanced or inflammatory breast cancer which is treatment-naïve
Intervention	Pertuzumab for 3 to 4 cycles in combination with neoadjuvant trastuzumab and chemotherapy
Comparator(s) (NZ context)	Neoadjuvant trastuzumab and chemotherapy
Outcome(s)	• A greater probability of pathologic complete response (pCR) • Improved event free survival, extrapolated from increased likelihood of pCR (Broglio et al. JAMA Oncol. 2016;2: 751-760). • Improved overall survival (extrapolated from increased likelihood of pCR) (Broglio et al. JAMA Oncol. 2016;2: 751-760).
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg. line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

7. Matters Arising – Special Authority applications from non-medical prescribers

Discussion

7.1. The Advisory Committee noted Pharmac had received a request from a medical oncologist and the Cancer Nurses College – Nurse Practitioners – Special Interest Group to allow Special Authority applications for oncology agents from nurse practitioners. The Committee noted prescriber competency management is the role of regulatory authorities under the Health Practitioners Competence Assurance Act 2003 (HPCA Act 2003). The Committee noted Pharmac was considering an amendment to remove prescriber restrictions for oncology and immunosuppressive agents, as well as supportive medications.

7.2. The Committee noted the discussion paper from Pharmac staff, detailing Pharmac's work on the consistent and appropriate use of prescriber restrictions in the Pharmaceutical Schedule. The Committee noted there have been regulatory changes in Aotearoa New Zealand which have supported the growth of non-medical prescribers, including nurse practitioners. The Committee noted that non-medical prescribers can legally prescribe medicines within their scope of practice under the HPCA Act 2003 however, for most oncology and immunosuppressive agents, non-medical prescribers are unable to apply for Special Authorities.

7.3. The Committee noted people access medical care differently and that prescriber restrictions often reflect the typical patient journey, where a person's care is commonly overseen by a medical specialist. However, there may be situations where a full array of specialists may not be available or where care is led by another practitioner. In these cases, prescriber restrictions may pose additional barriers for people trying to access funded medicines.

7.4. The Committee noted the multi-disciplinary nature of many healthcare teams in Aotearoa New Zealand. The Committee considered amendments to prescriber restrictions for oncology and immunosuppressive agents would support:

- health sector goals, including supporting people to access health services in the way that best suits them

- making the best use of the health workforce.

7.5. The Committee noted Pharmac staff are not aware of any evidence that indicates prescriber restrictions are valuable cost-management tools in the context of Pharmac's role funding medicines within a fixed budget. The Committee noted that there may be some instances in a patient treatment journey in which prescriber restrictions may limit some eligible people from accessing a funded medicine.

7.6. The Committee supported the reduction of access barriers for people with malignant disease, and to better reflect the multi-disciplinary nature of healthcare teams and the growth of non-medical prescribers.

7.7. The Committee considered review of current access criteria would enable refinement, to better articulate any need for specialist medical practitioner involvement (for example, for the confirmation of diagnosis and/or recommendation of treatment) and ensure there is consistent interpretation and application of access criteria across Aotearoa New Zealand. The Committee considered that it would be appropriate to consider the prescriber restrictions for oncology agents and welcomed future discussion papers for its consideration from Pharmac staff.

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

Application

8.1. The Committee reviewed the application from Janssen for subcutaneous daratumumab (Darxalex SC) in combination with bortezomib, cyclophosphamide and dexamethasone (D-VCd) for the treatment of people with newly diagnosed systemic light chain (AL) amyloidosis, following review of this application by PTAC in November 2021.

8.2. The Committee noted that Pharmac sought specific advice regarding the appropriateness of the biomarker endpoints for predicting longer term outcomes for this population group and the Special Authority criteria for this application.

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

Recommendation

8.4. The Committee **recommended** that daratumumab (intravenous or subcutaneous) in combination with bortezomib, cyclophosphamide and dexamethasone (D-CyBorD) be funded for the treatment of newly diagnosed systemic light chain (AL) amyloidosis with a **high priority,** within the context of treatments of malignancy, subject to the following Special Authority criteria:

> **DARATUMUMAB**
> **Initial application – (AL amyloidosis)** only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months for applications meeting the following criteria.
> All of the following:
> 1. Patient has systemic AL amyloidosis; and
> 2. Patient does not have multiple myeloma; and

3. Daratumumab is to be used in combination with bortezomib, cyclophosphamide and dexamethasone for week 1 to 24 and as a monotherapy from week 25 until disease progression.

Renewal – (AL amyloidosis) only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months.
All of the following:
1. Patient's condition has shown a partial haematologic response to treatment (see Note); and
2. The treatment remains appropriate, and the patient is benefitting from treatment.
Note: A partial haematologic response defined as at least a 50% reduction in the difference between involved and uninvolved free light chains.

8.5. In making this recommendation, the Committee considered:

8.5.1. The high health need of people with AL amyloidosis, especially those who are ineligible for autologous stem cell transplant (ASCT) and currently have no further treatment option to deepen their response.

8.5.2. The evidence of clinical response (deep and rapid haematologic response and organ improvement) and some evidence of quality of life (QOL) equivalence despite short trial follow-up. The Committee considered that good quality overall survival (OS) data would not eventuate due to crossover, however, that the endpoints for haematological and organ responses are robust surrogates for OS and that QOL benefits would be anticipated from organ responses long-term

8.5.3. That the addition of daratumumab SC to CyBorD for people with AL amyloidosis could slightly increase the number of individuals who could proceed to ASCT.

8.6. The Committee considered that it should revisit its advice to fund 24 months of treatment, as part of a new funding application, if further data regarding the benefit of treatment beyond 24 months were to eventuate in future.

Discussion

Māori Impact

8.7. The Committee noted that data to inform the impact of AL amyloidosis according to ethnicity is lacking, however, considered that Māori may experience a greater impact from the disease due to the higher rates of comorbidity and lower rates of autologous stem cell transplant (ASCT) in Māori with multiple myeloma compared with other population groups. The Committee considered that any treatment for AL amyloidosis that may increase the proportion of individuals who are candidates for transplant or lead to improve organ responses would likely be very beneficial for Māori.

Background

8.8. The Committee noted that the application for subcutaneous daratumumab (Darxalex SC) in combination with bortezomib, cyclophosphamide and dexamethasone (D-VCd; CyBorD) for the treatment of people with newly diagnosed AL amyloidosis was considered by PTAC in November 2021. At that time, PTAC recommended daratumumab (intravenous or SC) be funded for this indication with a medium priority and requested Pharmac seek advice from the Cancer Treatments Advisory Committee regarding appropriate stopping criteria, and views regarding use of a 12-month duration of approval in the Special Authority criteria for daratumumab for AL amyloidosis.

Need

8.9. The Committee noted that AL amyloidosis is generally associated with plasma cell dyscrasia in those with monoclonal gammopathy of undetermined significance (MGUS) and in multiple myeloma, with the aim of treatment for these conditions being reduction in light chain production by targeting plasma cells. The Committee noted that individuals can have both AL amyloidosis and multiple myeloma (although the ANROMEDA trial excluded patients with myeloma) and considered it important to consider daratumumab for those with both AL amyloidosis and multiple myeloma due to the overlap in their presentation and management. The Committee noted that organ dysfunction from amyloid deposits can preclude ASCT and that prognosis relates to the extent of organ dysfunction. The Committee noted that the treatment paradigm for multiple myeloma has been previously discussed and that treatment for AL amyloidosis in the context of MGUS consists of either bortezomib or thalidomide (not lenalidomide).

8.10. The Committee agreed with PTAC's views that people with AL amyloidosis have a high health need despite currently funded therapies. The Committee considered that this was especially true of those for whom transplant is unsuitable and currently have no further treatment option to deepen their response. The Committee reiterated the need for an effective therapy to reduce light chain production to prevent further organ dysfunction from AL amyloidosis. Members considered that more intensive induction therapy may also increase the number of individuals receiving an organ response and ultimately becoming candidates for transplant.

8.11. The Committee noted that PTAC estimated 10% of people with AL amyloidosis may be suitable candidates for ASCT, which aims to provide a deeper and more durable response. However, the Committee considered that approximately 20% was a more reasonable estimate given that some would become transplant candidates from organ responses obtained via induction therapy.

8.12. The Committee noted the rarity of AL amyloidosis (affecting approximately three per million in the population) and the absence of ethnicity data for New Zealand cases. The Committee noted that myeloma has a higher age-standardised incidence for Māori, who have younger age at presentation than non-Māori. Members considered it was unclear whether there was a difference in MGUS incidence or AL amyloidosis incidence according to ethnicity in New Zealand population groups.

8.13. The Committee considered that the extent of comorbidity in those with AL amyloidosis can impact on the degree of organ dysfunction and/or suitability for transplant, such as the combination of heart failure from ischemic heart disease and cardiac amyloidosis. The Committee considered that Māori may experience a greater impact from the disease due to the higher rates of comorbidity and noted that there are reduced rates of ASCT for Māori with myeloma compared with other population groups. The Committee considered that any treatment for AL amyloidosis that may increase the proportion of individuals who are candidates for transplant would likely be very beneficial for Māori.

Benefits and Suitability

8.14. The Committee noted that PTAC reviewed the key evidence for daratumumab SC in AL amyloidosis which comes from the randomised (1:1), open-label, active-controlled, multicentre, phase III ANDROMEDA study (Kastritis et al. N Engl J Med 2021;385:46-58; Kastritis et al. Presented at the 25th European Haematology Association (EHA25) Annual Congress 2020; Abstract Nr LB2604). ANDROMEDA included 388 patients with newly diagnosed AL amyloidosis with at least one organ impacted, cardiac stage I-IIIA disease (Mayo 2004), ECOG performance status of

less than three, and eGFR of at least 20 mL/min/1.73m^2. Participants received either bortezomib, cyclophosphamide and dexamethasone (CyBorD) then observation until major organ deterioration-PFS, or D-VCd (daratumumab SC plus CyBorD) with daratumumab SC maintenance until major organ deterioration-progression free survival (PFS) for a maximum of 24 cycles.

8.15. The Committee noted that the ANDROMEDA trial results were appraised by PTAC in November 2021, including the primary endpoint (haematologic complete response), and secondary endpoints including major organ deterioration-progression free survival (a composite endpoint), cardiac response, renal response, haematological progression, subsequent therapies and overall survival (OS). The Committee noted that a large proportion of the trial population received daratumumab post-progression and considered that this confounded the OS outcomes, although such a difference may not have been seen with the relatively short trial follow-up of median 11.4 months.

8.16. Members considered that haematologic, cardiac and renal outcomes were established in the literature as good surrogate outcomes for cardiac response and survival in AL amyloidosis, and that there was evidence of a link between depth of these responses and survival. The Committee was made aware of the following evidence supporting haematological response and cardiac biomarkers as acceptable surrogates for overall survival in AL amyloidosis:

8.16.1. An analysis of 816 patients with AL amyloidosis receiving first-line treatment in the EU and US reported that the extent of reduction of amyloidogenic free light chains (FLCs), and especially the depth of this response, was linked with survival at three months and six months (Palladini et al. J Clin Oncol. 2012;30:4541-9).

8.16.2. A prospective observational study of 915 patients with newly diagnosed AL amyloidosis who received bortezomib reported that haematologic response in FLCs and the depth of this response predicted survival (Manwani et al. Blood. 2019;134:2271-80).

8.16.3. A study of 94 patients with AL amyloidosis who had N-terminal pro-brain natriuretic peptide (NT-proBNP) measured at six months post treatment demonstrated a link between NT-proBNP response and survival in cardiac disease (Lilleness et al. Br J Haematol. 2020;188:424-7).

8.16.4. A further publication reporting whether NT-proBNP, troponin and NYHA response could predict survival in 248 patients with AL amyloidosis with renal failure; the authors considered that these were robust surrogates for cardiac dysfunction and prognosis noting the need to interpret this alongside eGFR (Palladini et al. Am J Hematol. 2012;87:465-71).

8.16.5. A study of 416 patients with newly diagnosed AL amyloidosis reporting that deeper organ (heart, kidney, liver) response was associated with better survival (Muchtar et al. Blood. 2017;130(Suppl_1):3154).

8.17. The Committee noted that long-term efficacy data for daratumumab in AL amyloidosis is not yet available, however, considered it reasonable to infer from the duration of response seen in long-term data for multiple myeloma. The Committee noted the time to maximum organ response in AL amyloidosis of 24 or 30 months (Muchtar et al. Blood 2017; 130 (Supplement 1): 3154). The Committee noted that ANDROMEDA already reported substantial organ improvement from the reduction in

light chains despite the trial's short follow-up duration and considered that the ongoing organ responses would be expected to improve with further time. The Committee therefore considered that daratumumab would provide durable organ responses in AL amyloidosis. Further, the Committee considered that improved quality of life (QOL) would be expected given that deeper organ responses are assumed to be associated with both survival and better QOL.

8.18. The Committee noted that treatment of multiple myeloma is less efficacious in subsequent lines and considered it reasonable to assume that people with AL amyloidosis would also experience less durable and deeper responses in later lines of therapy as the biologic rationale is similar for both diseases. Members considered that increasing rates of treatment resistance would likely develop in later lines of therapy and that it would be reasonable to use multiple myeloma data to model this in AL amyloidosis.

8.19. Overall, the Committee considered that there was good evidence of meaningful clinical responses (deep and rapid haematologic response and organ improvement) with some evidence of QOL equivalence, although noting the short trial follow-up duration. The Committee considered that good quality OS data would not be expected to eventuate due to crossover. However, the Committee considered that the endpoints for haematological and organ responses are robust surrogates for OS in this context and that QOL benefits would be anticipated from organ responses in the long term.

Costs and Savings and Special Authority criteria

8.20. The Committee considered that, under the proposed Special Authority criteria, the number of people eligible would be small (ie three per million per year). The Committee considered that should daratumumab be funded for multiple myeloma in the second line setting, if funded for AL-amyloidosis, it would be reasonable to limit access to daratumumab to once per lifetime of the individual, regardless of the indication for which it is funded.

8.21. The Committee considered that it would be difficult to differentiate between AL amyloidosis and multiple myeloma, if daratumumab were funded for either indication. The Committee considered that the Special Authority criteria should limit the ability to receive daratumumab for both multiple myeloma and AL amyloidosis on separate occasions (eg individuals with multiple myeloma who had already been treated with daratumumab should not also receive funded daratumumab for AL amyloidosis).

8.22. The Committee considered that reduction in light chains is critical to treatment success and improvement in AL amyloidosis and therefore considered that funded treatment with daratumumab for this population should stop upon haematological progression or cease based on a lack of haematological response at three months, noting the median time to haematological response of 60 days in ANDROMEDA.

8.23. The Committee noted that people in the ANDROMEDA trial were treated with daratumumab for a maximum of 24 months. The Committee was made aware of a retrospective analysis of 15 patients with AL amyloidosis who received daratumumab monotherapy and dexamethasone for at least 2 months before discontinuing after achieving a complete response. The Committee noted that this study reported no significant difference in the time to next treatment or death between the group with time limited daratumumab and those who recieved continuous maintenance (Chung et al. Blood. 2019;134(Suppl_1):1884). The Committee therefore considered it reasonable to fund 24 months' treatment as supported by the trial evidence, given

that the benefit of treatment beyond 24 months was unclear from the data available at this time, but considered that this should be revisited as part of a new funding application if further data were to eventuate in future.

8.24. Members considered that treatment with daratumumab could increase the number of individuals with AL amyloidosis who could proceed to ASCT by approximately 10% (therefore 30% of this population) but that this was unlikely to be hugely impactful to the health sector due to the overall small numbers concerned.

8.25. Members noted an economic assessment by Canada's Drug and Health Technology Agency (CADTH) of daratumumab for AL amyloidosis, which modelled treatment benefit based on haematological response data from ANDROMEDA and evidence from Kastritis et al. (Amyloid. 2020;28:3-11) on OS associated with different levels of hematologic response. The Committee considered this modelling approach was appropriate for use in Pharmac's assessment of daratumumab for this indication given the lack of available long-term OS data from ANDROMEDA.

Summary for Assessment

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

Population	People with systemic light chain (AL) amyloidosis
Intervention	D-VCd (D-CyBorD) = daratumumab (IV or SC), bortezomib, cyclophosphamide and dexamethasone x 6 cycles followed by daratumumab (IV or SC) until disease progression/max 24 cycles. Daratumumab administered as follows: - Weeks 1-8 given weekly (8 doses) - Weeks 9-24 given every 2 weeks (8 doses) - Weeks 25 onwards given every 4 weeks until disease progression or a maximum duration of 24 months Median treatment duration of 38 weeks.
Comparator(s)	VCd (CyBorD)= bortezomib, cyclophosphamide and dexamethasone x 6 cycles or maximum response
Outcome(s)	• Improved haematological response rate • Improved major organ deterioration progression-free survival • No direct evidence of survival benefit from ANDROMEDA; survival benefit is likely based on increased response rate and association between haematological response and overall survival • Quality of life – likely a small effect in short term for global health status and fatigue score with D-VCd; greater uncertainty about magnitude of long-term quality of life benefit (although expected to improve with long-term organ responses). • Increased number of individuals with AL amyloidosis who could proceed to ASCT (by approximately 10%) ANDROMEDA found the percentage of daratumumab (D-VCd) treated patients who experienced haematological complete response, was 53% vs. 18% of VCd. The study also found a hazard ratio for major organ deterioration of 0.58 for D-VCd treated patients vs. VCd.

Table definitions:

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

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

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

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

9. Pembrolizumab for the first-line treatment of unresectable or metastatic carcinoma of the oesophagus or gastroesophageal junction

Application

9.1. The Advisory Committee reviewed the application for pembrolizumab for the first-line treatment of unresectable or metastatic carcinoma of the oesophagus or gastroesophageal junction.

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

Recommendation

9.3. The Advisory Committee **recommended** that the use of pembrolizumab for the first-line treatment of individuals with metastatic carcinoma of the oesophagus or gastroesophageal junction be **deferred** pending a review of the entire oesophageal cancer treatment setting.

Discussion

Māori Impact

9.4. The Committee noted that oesophageal cancer affects Māori at a higher rate than non-Māori, and that Māori are often diagnosed at a later disease stage. The Committee also noted that while Māori who are diagnosed with oesophageal cancer have comparable one-year survival rates (42% in 2010-11) compared to non-Māori (39%), they have poorer five-year (5.4% for Māori and 11.6% for non-Māori in 2010-2011) and cumulative relative survival rates (Ministry of Health NZ. Cancer Patient Survival. 2015).

9.5. The Committee considered that funding pembrolizumab for the requested indication would support improved health outcomes for Māori with oesophageal cancer, by providing another line of treatment in the metastatic setting, with a reduced toxicity profile compared to chemotherapy.

Health need

9.6. The Committee noted that the total incidence of oesophageal cancer amongst males in New Zealand and Australia was 5.4 per 100,000 in 2012, with an age-standardised mortality rate of 4.7 per 100,000 (incidence to mortality ratio 1.3; Wong et al. Sci Rep. 2018;8:4522). The Committee considered this estimate to be conservative since it was higher than other available estimates. The Committee noted that for females the incidence and mortality rates were 1.7 and 1.3 per 100,000, respectively (incidence to mortality ratio 1.2). The Committee noted that, according to data from the Ministry of Health, the age standardised mortality rate for oesophageal cancer was 2.8/100,000 in 2017. The Committee noted that oesophageal cancer usually occurs in people over the age of 60, and that the five-year cumulative relative survival is 11.8% (Ministry of Health NZ. Cancer Patient Survival. 2015).

9.7. The Committee noted that oesophageal cancer affects Māori at a rate 1.64 times higher than non-Māori (Robson et al. 2006. Unequal Impact: Māori and non-Māori Cancer Statistics 1996-2001. Ministry of Health, New Zealand), and that Māori are often diagnosed at a later stage of disease. The Committee also noted that while Māori who are diagnosed with oesophageal cancer have comparable one-year survival rates (42% in 2010-11) compared to non-Māori (39%), they have poorer five-year (5.4% for Māori and 11.6% for non-Māori in 2010-2011) and cumulative relative survival rates (Ministry of Health NZ. Cancer Patient Survival. 2015).

9.8. The Committee noted that there are two main types of oesophageal cancer, squamous cell carcinoma or adenocarcinoma, each with different risk factors. The Committee noted that although adenocarcinoma of the oesophagus is considered to be rarer than squamous cell carcinoma worldwide, the majority of oesophageal cancer registrations in New Zealand are adenocarcinomas (Morgan et al. Gut. 2021. 70:234-42). The Committee noted that in New Zealand, the incidence of oesophageal adenocarcinoma has been reported as 4.0 per 100,000 person years for men and 1.5 per 100,000 person years for women, while the incidence of squamous cell carcinoma was 1.5 per 100,000 person years for men and 1.2 per 100,000 person

years for women (Arnold et al. Gut. 2015;64:381-7; Wong et al. Sci Rep. 2018;8:4522; data from 2012 for both).

9.9. The Committee noted that the ICBP SURVMARK-2 project, a comparison of international cancer survival, reported that adenocarcinoma disproportionately affects males in New Zealand, while squamous cell carcinoma affects males and females equally (Arnold M, Rutherford M, Lam F, Bray F, Ervik M, Soerjomataram I (2019). ICBP SURVMARK-2 online tool). The Committee noted that data on the extent of disease at point of diagnosis in rural New Zealand, and by deprivation, is lacking.

9.10. The Committee noted that treatment for oesophageal cancer in New Zealand has remained the same for decades, and that there is a significant unmet health need for those affected. The Committee noted that the current treatment for people with oesophageal cancer (if surgery is unsuccessful or inappropriate) is usually systemic chemotherapy containing a platinum-based compound with a fluoropyrimidine; 5-FU + cisplatin and FOLFOX (5-FU, oxaliplatin and leucovorin/folinic acid), though cisplatin + capecitabine and oxaliplatin + capecitabine are also used. The Committee noted that second-line treatments include cisplatin, docetaxel, continued 5-FU, paclitaxel, oxaliplatin and irinotecan in the New Zealand setting. The Committee noted that current therapies are considered palliative at advanced stages of disease.

9.11. The Committee noted that family and whānau of individuals with oesophageal cancer are also affected, especially with regard to their emotional wellbeing in seeing their family member's health decline, and also the time and cost associated with accompanying them to chemotherapy sessions and having to regularly miss work.

Health Benefit

9.12. The Committee noted that pembrolizumab is an immune checkpoint inhibitor, which binds to the PD-1 receptor on T-lymphocytes, blocking the effects of the PD-L1 and PD-L2 ligands. By blocking the PD-1 receptor, the PD-L1 and PD-L2 ligands are prevented from attaching, and the tumour cell is therefore exposed to the immune system. The Committee noted that the primary evidence for pembrolizumab in the first-line treatment of unresectable or metastatic oesophageal cancer comes from the phase III KEYNOTE-590 trial comparing pembrolizumab in combination with chemotherapy to chemotherapy alone (Sun et al. Lancet. 2021;398:759-71).

9.13. The Committee noted that the participants in KEYNOTE-590 were primarily of Asian ethnicity, and that the majority of patients had squamous cell carcinoma (73%). The Committee also noted that inclusion criteria specified an ECOG performance status of 0-1, previously untreated RECIST measurable disease, and that tissue was required for PD-L1 immunohistochemical analysis (combined positive score [CPS]; 52% of squamous cell carcinoma participants had a CPS score ≥10). The Committee noted that participants were treated with either intravenous pembrolizumab 200 mg three-weekly with chemotherapy (intravenous cisplatin 80 mg/m^2 three-weekly and 5-flurouracil 800 mg/m^2/day continuous intravenous infusion on each of Days 1 to 5 three-weekly, total of 4.000 mg/m^2 per 3-week cycle) or placebo with chemotherapy. The Committee noted that participants were not stratified by PD-L1 status.

9.14. The Committee noted that the mean treatment duration was 7.7 months for the pembrolizumab arm and 5.8 months for the chemotherapy alone arm, though there was some uncertainty in the duration individual treatment administered in each treatment arm. The Committee also noted that the median follow-up for the trial was 22.6 months. The Committee noted that overall survival for oesophageal squamous cell carcinoma with a CPS score of ≥10 at 22.6 months was 31% in the

pembrolizumab arm versus 15% in the placebo arm (hazard ratio [HR] 0.57; 95% CI 0.43 to 0.75; p<0.0001). The Committee noted that the overall survival for oesophageal squamous cell carcinoma regardless of CPS was 29% for the pembrolizumab arm versus 17% for the placebo arm (HR 0.72; 95% CI 0.60 to 0.88; p=0.0006); and that the overall survival for all participants (squamous cell carcinoma and adenocarcinoma) with a CPS of ≥10 was 31% in the pembrolizumab arm and 15% in the placebo arm (HR 0.62; 95% CI 0.49 to 0.78; p<0.0001). The Committee noted that for all of the trial participants, regardless of tumour type or CPS score, overall survival was 28% in the pembrolizumab arm and 16% in the placebo arm (HR 0.73; 95% CI 0.62 to 0.86; p<0.0001).

9.15. The Committee noted that the median overall survival for patients with PD-L1 CPS <10% was 10.5 months in the pembrolizumab arm versus 10.6 months in the placebo arm (HR 0.86; 95% CI 0.68 to 1.1). The Committee also noted the results from an unplanned post-hoc analysis of patients with adenocarcinoma, which was underpowered to detect statistical significance. This analysis showed no statistically significant difference between treatment arms (HR for overall survival 0.74; 95% CI 0.54 to 1.02). The Committee considered that this may be due to adenocarcinomas usually not expressing PD-L1 highly. The Committee noted that there were no new adverse event indications for pembrolizumab that have not already been noted for other indications.

9.16. The Committee considered that the KEYNOTE-590 trial was of good quality and strength. The Committee considered, however, that the trial population (predominantly of Asian ethnicity and with squamous cell carcinoma) does not necessarily reflect the New Zealand affected population. The Committee also considered that performance status in the trial (ECOG 0-1) would not necessarily represent those in New Zealand with unresectable or metastatic oesophageal cancer which is a high burden disease. The Committee considered that in the New Zealand context, individuals so affected are likely to have worse performance status at this disease stage. The Committee also considered that it would not be appropriate in this context to consider giving a five-day continuous infusion of 5-FU in an inpatient setting, as this would not be suitable or safe for those with advanced disease. The Committee agreed that it would be necessary to seek further information about the current treatment landscape in New Zealand which would form the best treatment to recommend for funding and the nature of the 'chemotherapy backbone' of the proposed treatment, before proceeding with an economic assessment of the proposal.

9.17. The Committee also noted the following evidence relating to other PD-L1 inhibitors for the treatment of oesophageal cancer:

9.17.1. CheckMate649 (ClinicalTrials.gov Identifier: NCT02872116); Janjigian et al. Lancet. 2021;398:27-40: First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma.

9.17.1.1. Shitara et al. Nature. 2022;603:942-8: Nivolumab plus chemotherapy or ipilimumab in gastro-oesophageal cancer

9.17.2. CheckMate648 (ClinicalTrials.gov Identifier: NCT03143153);

9.17.2.1. Doki et al. N Engl J Oncol. 2022;386:449-62: Nivolumab Combination Therapy in Advanced Oesophageal Squamous-Cell Carcinoma

9.17.3. ATTRACTION-4 (ClinicalTrials.gov Identifier: NCT02746796):

9.17.3.1. Kang et al. Lancet Oncol. 2022;23:234-47: Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer

9.17.4. CheckMate032 (ClinicalTrials.gov Identifier: NCT01928394):

9.17.4.1. Janjigian et al. J Clin Oncol. 2018;36:2836-44: Efficacy and Safety of Nivolumab and Nivolumab Plus Ipilimumab in Patients With Metastatic Esophagogastric Cancer.

9.18. The Committee considered that there may be a possibility of a class effect for immune checkpoint inhibitors in the treatment of oesophageal cancer, and that there would be a benefit in considering the oesophageal cancer treatment landscape (including a class effect for immune checkpoint inhibitors for this indication) at a future meeting.

Suitability

9.19. The Committee noted that pembrolizumab adds a minimum of 30 minutes to infusion time additional to the chemotherapy being received.

9.20. The Committee noted that pembrolizumab can be offered as three- or six-weekly treatment, which may be more convenient for those being treated and their whānau, however noting that chemotherapy infusions would still be required at three-weekly intervals.

Cost and Savings

9.21. The Committee considered that of the approximately 320 oesophageal cancer registrations annually in New Zealand, 250 would have locally advanced or metastatic oesophageal cancer. 51% of that group was noted to be eligible for pembrolizumab under the criteria proposed by the supplier, based on CPS≥10, though the Committee considered that the relationship observed between CPS and treatment outcomes in a post-hoc analysis of KEYNOTE-590 may not be adequate to qualify CPS as an appropriate biomarker for use in the Special Authority criteria.

9.22. The Committee considered that funding of pembrolizumab would also add additional costs to the health sector with the need for additional imaging (three-monthly CT scans), disease monitoring (monthly consultation visits) and burden on infusion centres. The Committee also considered that the use of pembrolizumab in the requested setting will increase the burden on laboratory and diagnostic testing services (three-weekly full blood count, renal function, and hepatic function tests) and PD-L1 testing for both those treated and people considered for treatment (if CPS testing were included in the eligibility criteria for pembrolizumab). The Committee considered that inpatient admissions for adverse events of grade 3 or above would not substantially change, given the relative rates of adverse events in the two treatment arms of KEYNOTE-590.

9.23. The Committee considered that the uptake of pembrolizumab, if funded for the requested indication, would be upwards of 90% for individuals with good performance status. The Committee considered that, at first, there would be a small prevalent bolus of individuals diagnosed in the few months before funding who would require

treatment with pembrolizumab immediately, followed by those starting treatment as incidence occurs.

Funding Criteria

9.24. The Committee noted that the results reported from KEYNOTE-590 indicate that pembrolizumab is not as effective for the treatment of adenocarcinoma as it is for squamous cell carcinoma. The Committee also noted that the proportion of adenocarcinoma in New Zealand is much higher than what was represented in the trial.

9.25. The Committee noted that KEYNOTE-590 excluded individuals who had progressed within six months of receiving prior neoadjuvant/adjuvant therapy. The Committee considered that appraisal of pembrolizumab in this context would require additional data.

9.26. The Committee considered it would be appropriate for pembrolizumab to be used in the treatment of stage I oesophageal cancer which has relapsed following surgery and has not been treated with chemotherapy, as this population was included in KEYNOTE-590. The Committee also considered that those with unresectable and previously untreated stage II-III oesophageal cancer may benefit from treatment with pembrolizumab.

9.27. The Committee considered that pembrolizumab treatment may also be suitable for individuals who have had surgery, with or without neoadjuvant treatment, and then relapsed within six months. The Committee noted however that this post-surgical group was excluded from the KEYNOTE-590 trial and considered that there is not enough evidence available to evaluate the benefit of pembrolizumab for these individuals. The Committee considered that the use of pembrolizumab, or another immune checkpoint inhibitor, in the treatment of these individuals should be reconsidered in the context of the entire oesophageal carcinoma treatment landscape.

Summary for Assessment

9.28. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for pembrolizumab if it were to be funded in New Zealand for the first-line treatment of unresectable or metastatic carcinoma of the oesophagus or gastroesophageal junction. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Adults with carcinoma of the oesophagus or gastroesophageal junction, with the following characteristics: • Stage III or IV disease • No prior systemic therapy (ie 1L treatment) • Disease which is not amenable to surgical resection or definitive chemoradiation • CPS score ≥10 • ECOG performance status of 0-2 • Any disease subtype, including people with adenocarcinoma of any Siewert classification
Intervention	Per KEYNOTE-590: • Pembrolizumab 200 mg fixed dose administered intravenously (IV) over 30 minutes on Day 1 of each 3 week cycle, ceased at the sooner of progression or 35 administrations AND • Cisplatin 80 mg/m^2 IV on Day 1 of each 3 week cycle, ceased at the sooner of progression or 6 administrations AND • Fluorouracil (5 FU) 800 mg/m2/day continuous IV infusion on each of Days 1 to 5 Q3W (total of 4.000 mg/m^2 per 3-week cycle), capped at the sooner of progression or 35 administrations Mean duration of treatment of 11 cycles (KEYNOTE-590).
Comparator(s)	Per KEYNOTE-590: • Cisplatin 80 mg/m^2 IV on Day 1 of each 3 week cycle, ceased at the sooner of progression or 6 administrations AND • 5 FU 800 mg/m2/day continuous IV infusion on each of Days 1 to 5 Q3W (total of 4.000 mg/m^2 per 3-week cycle), capped at the sooner of progression or 35 administrations Mean duration of treatment of 8.5 cycles (KEYNOTE-590).

Outcome(s)	The therapeutic intent of pembrolizumab in this indication is to:
	
	• improve overall survival (OS)
	  ○ 13.5 months pembro + SOC vs. 9.4 months SOC – 4 months gain (KEYNOTE-590)
	• improve health-related quality of life (HRQOL) by prolonging progression free survival (PFS).
	  ○ 7.5 months pembro + SOC vs. 5.5 months SOC – 2 months gain (KEYNOTE-590)

Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg. line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

10. Trastuzumab for the treatment of locally advanced or metastatic gastric cancer

Application

10.1. The Advisory Committee reviewed the application for trastuzumab for the treatment of locally advanced or metastatic gastric cancer.

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

Recommendation

10.3. The Advisory Committee **recommended** that trastuzumab for the treatment of locally advanced or metastatic gastric cancer be listed with a **high priority** within the context of treatment of malignancy, subject to the following Special Authority criteria:

> **Initial application** — (locally advanced or metastatic gastric cancer) only from a relevant specialist or relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for application meeting the following criteria:
> All of the following:
> 1) The patient has locally advanced or metastatic gastric cancer expressing HER-2 IHC 2+FISH+ or IHC3+; and
> 2) Patient has an ECOG score of 0-2.
>
> **Renewal** — (locally advanced or metastatic gastric cancer) only from a relevant specialist or relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:
> Both:
> 1) The cancer has not progressed at any time point during the previous 12 months whilst on trastuzumab; and
> 2) Trastuzumab to be discontinued at disease progression.

10.4. In making this recommendation, the Advisory Committee noted the high health needs relating to the significant symptom burden and modest survival from gastric cancer, the apparent survival advantage from treatment with trastuzumab and likely reduced health resource usage, and the significant cost impact of use of biosimilar trastuzumab in this indication, and the likely reduction in price of trastuzumab following the current competitive process.

Discussion

Māori Impact

10.5. The Committee discussed the impact of funding trastuzumab for the treatment of gastric cancer on Māori health areas of focus and Māori health outcomes. The Committee noted that Māori experience a significantly higher rate of stomach cancer than non-Māori and that Māori also experience a significantly higher mortality rate from stomach cancer compared to non-Māori (Te Aho report. 2020).

10.6. The Committee noted that a study from 2017 reported that approximately half of Māori with stomach cancer had diffuse stomach cancer (Ellison-Loschmann et al. PLoS One. 2017;12:e0181581), and that BPAC reported in 2018 that approximately 13% of advanced diffuse gastric cancers in Māori are hereditary.

Background

10.7. The Committee noted that an application for trastuzumab for the treatment of HER2-positive gastric cancer was reviewed by PTAC (recommended for funding with a low priority) and the Cancer Treatments Advisory Committee (at the time "CaTSoP", recommended for decline) in 2011. The Committee noted that, in 2011, the clinical relevance of the survival benefits seen in the pivotal ToGa trial (Bang et al. Lancet. 2010;376:687-97) were unclear.

10.8. The Committee noted that since 2011, more evidence has become available for the use of trastuzumab in the treatment of gastric cancer. The Committee also noted that, at a CTAC meeting in April 2022, the Committee supported a competitive process for the supply of trastuzumab, and considered that further assessment of the use of trastuzumab in gastric cancer was warranted.

Health Need

10.9. The Committee noted that according to the 2018 new cancer registration data from the Ministry of Health (Manatū Hauora), stomach cancer occurs at a rate of 5.3 per 100,000 in New Zealand, with the total number of registrations at 408 for that year. The Committee also noted that mortality data from 2017 indicates that 288 New Zealanders died from stomach cancer that year, 47 of which were Māori. The Committee also noted that a further 90 New Zealanders likely died from cancer of the gastro-oesophageal junction in that year.

10.10. The Committee noted that according to Ministry of Health New Zealand Cancer Registry data, in 2021 85 of the total 500 stomach cancer registrations were Māori, and 48 were of Pacific ethnicity. The Committee noted that data from Qlik also reports that, for "lower third oesophageal cancer registrations", 19 registrations out of a total of 183 were for individuals who were of Māori ethnicity and 3 were of Pacific ethnicity. The Committee considered that it was reasonable to assume that all cancer registrations for the lower third of the oesophagus would be considered part of the gastro-oesophageal junction and therefore eligible for treatment with trastuzumab.

10.11. The Committee noted that globally the vast majority of gastric cancers are adenocarcinomas, which can be further subdivided into intestinal and diffuse type, with intestinal-type gastric cancer being more common in older individuals and more strongly associated with exposure to environmental risk factors. The Committee noted that diffuse-type gastric cancer is more associated with an earlier onset and a family history of the disease. The Committee also noted that HER2-positivity is predominantly seen in intestinal type gastric cancer, with a low prevalence in diffuse type gastric cancer (32% vs. 6%; Gravalos C. Jimeno A. Ann Oncol. 2008;19:1523-9).

10.12. Although the rate of stomach cancer for both Māori and non-Māori has nearly halved over the last 20 years, the Committee noted that compared with non-Māori, Māori experience significantly higher rates of both stomach cancer incidence and mortality from stomach cancer compared to non-Māori (Te Aho report. 2020). The Committee noted that a study from 2017 reported that approximately half of Māori with stomach cancer had diffuse stomach cancer (Ellison-Loschmann et al. PLoS One. 2017;12:e0181581), and that BPAC reported in 2018 that approximately 13% of advanced diffuse gastric cancers in Māori are hereditary.

10.13. The Committee noted that Pacific peoples also experience higher rates of both incidence and mortality in relation stomach cancer compared with New Zealand Europeans. The Committee noted that in addition to genetic factors, Māori and Pacific peoples' have an increased exposure to environmental risk factors for gastric cancer, and their health outcomes from gastric cancer are further compromised by the late stage of the cancer at diagnosis, limited access to endoscopy services outside of main centres.

10.14. The Committee noted that the initial symptoms of gastric cancer are often non-specific, and that progressive gastric cancers lead to nutritional decline, difficulty

swallowing, and a rapidly declining performance status. The Committee also noted that gastric cancer is associated with a high level of carer burden.

10.15. The Committee noted that currently, treatment options for gastric cancer in New Zealand are limited, with those affected generally receiving doublet chemotherapy, with response rates at about 50%, and a duration of response limited to six-nine months. The Committee noted that generally individuals are usually only able to be treated with one line of treatment and/or palliative care. The Committee noted that in New Zealand treatment would be either Xelox (capecitabine and oxaliplatin) or FOLFOX (folinic acid, fluorouracil, and oxaliplatin). The Committee considered that use of triplet chemotherapy is generally rare (owing to increased toxicity with marginal incremental benefit), and that very few would have triplet chemotherapy in New Zealand.

10.16. The Committee noted that internationally, treatment of gastric cancer is often driven by biomarker status (eg HER-2, dMMR +/-, PD-L1 status).

Health Benefit

10.17. The Committee noted that trastuzumab is a monoclonal antibody that targets the HER2 receptor, inducing antibody-dependent cellular cytotoxicity, inhibiting HER2-mediated signalling, and preventing cleavage of the extracellular domain of HER2.

10.18. The Committee noted again the primary trial for trastuzumab in combination with chemotherapy compared with chemotherapy alone in the treatment of gastric cancer (ToGa trial) which recruited 594 patients with inoperable, locally advanced, recurrent, and/or metastatic HER2-positive cancer of the stomach or the gastro-oesophageal junction. The Committee noted that the median overall survival for the total trial population was 13.8 months with trastuzumab compared to 11.1 months for those treated with chemotherapy alone (hazard ratio [HR] 0.74; 95% CI 0.60 to 0.91; p=0.0046). The Committee noted that for patients with high HER2 expression (IHC 2+ and FISH-positive tumours or IHC 3+ tumours) the median overall survival was 16.0 months with trastuzumab treatment, versus 11.8 months with chemotherapy alone (HR 0.65; 95% CI 0.51 to 0.83). The Committee noted that the benefit of trastuzumab treatment is greater for patients with higher HER2 expression, with the greatest benefit seen in those with IHC 3+/FISH positive patients.

10.19. The Committee noted that the addition of trastuzumab to cisplatin and 5FU-based therapy increased response rates from 35% to 47%. The Committee also noted that the toxicities were similar between treatment arms, with a minor increase in grade 3-4 diarrhoea and asymptomatic reduction in left ventricular ejection fraction with trastuzumab.

10.20. The Committee noted the following additional evidence for the use of trastuzumab in the treatment of gastric cancer:

10.20.1. Gong et al. MBC Cancer. 2016;16:68 CGOG 1001: an open-label, multicenter, prospective phase II study (n=51) of trastuzumab in combination of oxaliplatin and capecitabine in which 66.5%of participants responded to treatment.

10.20.2. Mondaca et al. Gastric Cancer. 2019;22:355-62: a single-arm multicentre phase II study (n=26) of trastuzumab in combination with docetaxel and 5-flurouracil in which the objective response rate was 65%, and the toxicity profile was high.

10.20.3. Rivera et al. Cancer Chemother Pharmacol. 2019;83:1175-81 HERXO: a multicentre, prospective, non-randomised, non-controlled, open-label national (Spanish) phase II study (n=45) of trastuzumab in combination with oxaliplatin and capecitabine which reported a 46.7% response rate.

10.20.4. Yuki et al. Cancer Chemother Pharmacol. 2020;85:217-23 SOX: a multicentre, open-label, single arm, phase II trial (n=39) of trastuzumab in combination with oxaliplatin and S-1 which reported an 82.1% response rate.

10.20.5. Takahari et al. Gastric Cancer. 2019;22:1238-46: a multicentre, prospective, single-arm phase II study (n=75) of trastuzumab in combination with oxaliplatin and S-1 which reported an objective response rate of 70.7%.

10.21. The Committee also noted a meta-analysis comparing the chemotherapy backbones for first-line trastuzumab treatment-containing regimens for HER2-postive advanced oesophagogastric cancer (Ter Veer et al. Int J Cancer. 2018;143:438-48) which reported an overall survival advantage with oxaliplatin versus cisplatin (20.7 months versus 16 months, respectively; HR 0.75). The Committee noted that oxaliplatin regimens are also less toxic than cisplatin regimens. The Committee considered that the difference in overall survival in the meta-analysis compared to the ToGa trial is likely due to the improvement in best supportive care since publication of the ToGa trial.

10.22. The Committee noted that the evidence indicates an advantage for an oxaliplatin doublet, such as Xelox or FLOFOX, rather than the ToGa regimen of cisplatin with 5-FU. The Committee considered that triplet regimens show no additional survival benefit and have worse toxicity profiles.

10.23. The Committee considered that if trastuzumab were to be funded in this setting, there would be a slight decrease in demand on family support and palliative care services. The Committee considered that those who progress following treatment with a trastuzumab containing regimen in the first line, would then be treated with a taxane chemotherapy.

Suitability

10.24. The Committee noted that use of trastuzumab in this setting would add an additional 30 minutes to an already prolonged chemotherapy administration regimen but considered that this would not impact the number of people with gastric cancer receiving treatment in this setting. The Committee noted that there was no evidence currently available for the use of subcutaneous trastuzumab in the treatment of gastric cancer.

Cost and Savings

10.25. The Committee noted that in the last three years in New Zealand, there was an average incidence of 640 cases of gastric cancer annually, comprising both stomach cancers and cancers of the lower third of the oesophagus. The Committee considered approximately 65% of cases would be of an advanced stage, and of the approximately 400 advanced gastric cancer cases, 80 would be expected to be HER2-positive.

10.26. The Committee noted the Pharmac estimate of 1.5 hospitalisations and 0.7 Emergency Department visits per patient per year with gastric cancer, based on the

publication by Abraham et al. (Future Oncol 2021;17: 291-99). The Committee noted that few of the patients in this publication were treated with trastuzumab, and that health resource utilisation would be expected to be lower with trastuzumab, given improved response rates to treatment and better performance status.

10.27. The Committee noted the high cost of treatment when first considered in 2011, and considered that the ongoing competitive process for intravenous trastuzumab is likely to result in a much more favourable cost to the health system.

10.28. The Committee noted that those on treatment would be assessed by a specialist every three weeks while on chemotherapy, and if continued on maintenance trastuzumab this would be every three-six weeks. The Committee noted that trastuzumab use would increase the need for cardiac testing in the form of multigated acquisition (MUGA) scan or echocardiogram, which would have to be performed every three months.

Funding Criteria

10.29. The Committee considered that the evidence suggests that the greatest benefit for trastuzumab in the treatment of gastric cancer is in those with 'high' HER2-positivity (ie high expression of HER2 as defined by IHC2+/FISH+ or IHC3+) and considered it appropriate to restrict trastuzumab treatment to those with high expression. The Committee noted that HER2 expression testing varies across centres and considered that due to the intra-tumoral heterogeneity of these cancers, multiple biopsies are needed to ensure sufficient tissue is collected. The Committee noted that many biopsy specimens are found to be necrotic in nature or don't contain tumour and considered that these can be used as negative controls. The Committee noted that there is currently no formal consensus relating to the number of endoscopic biopsies required for HER2 testing, with international guidance ranging from four to eight.

Summary for Assessment

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

Population	People with locally advanced or metastatic gastric cancer, with 'high' HER2 expression (defined as IHC 2+/FISH positive, or IHC 3+)
Intervention	Trastuzumab in combination with doublet therapy Trastuzumab administered at a dose of 8mg/kg on day 1, followed by 6mg/kg every 3 weeks until disease progression or unacceptable toxicity Chemotherapy comprised typically of Xelox/FOLFOX Based on the ToGA trial, assume approximately 45% of patients receive post-study chemotherapy (see Supplementary Table 1 of key publication).
Comparator(s)	Doublet chemotherapy, in the form of Xelox/FOLFOX

Outcome(s)	Trastuzumab was reported to result in improved OS and PFS vs doublet chemotherapy in the ToGA trial (hazard ratio for OS 0.74, hazard ratio for PFS 0.71) Among those with high HER2 expression, hazard ratio for OS 0.65, median OS 16.0 months with trastuzumab vs 11.8 months with chemotherapy - No PFS information available for the high HER2 expression subgroup, though it is likely that PFS would also be longer in this group

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

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

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

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

11. Abiraterone and co-prescribed glucocorticoids

Application

11.1. The Committee noted that Pharmac sought the Committee's advice on the potential appropriateness of transitioning people with prostate cancer currently taking prednisone onto a different corticosteroid (eg prednisolone) instead, and potentially as part of a change to a generic abiraterone acetate product.

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

Recommendation

11.3. The Committee considered that it would be appropriate for Pharmac to progress a competitive process for abiraterone acetate that could result in the funding of a generic abiraterone acetate with a different corticosteroid (ie not prednisone) for all individuals currently receiving or initiating funded treatment with abiraterone acetate.

11.4. In making this consideration, the Committee:

11.4.1. Noted the available evidence indicated that equivalent corticosteroid doses were interchangeable in this context with no therapeutic differences expected.

11.4.2. Considered that there would be no impact for people starting on treatment, who commenced treatment with a generic abiraterone acetate and a different corticosteroid partner.

11.4.3. Considered that people switching to a funded generic abiraterone acetate with a different corticosteroid partner would benefit from prescriber education regarding the evidence for corticosteroid dose equivalence and information to support prescriber discussions with those receiving treatment.

11.4.4. Considered that Pharmac could investigate supporting the implementation of such a switch with pharmacist alerts to review prescriptions for abiraterone acetate and corticosteroids.

11.5. The Committee considered that it would like to review its recommendations for proposals for abiraterone acetate based upon any future price changes, given that the anticipated cost was a factor in some of the Committee's previous recommendations for this medicine.

Discussion

Māori Impact

11.6. The Committee noted that in April 2022, the Committee had noted that Māori experience worse outcomes from prostate cancer than non-Māori and considered that Māori would receive benefit from increased access to suitable treatments in earlier lines of therapy.

Background

11.7. The Committee noted that abiraterone acetate (brand name Zytiga) is currently funded for metastatic CRPC (mCRPC) and that there is an active patent in New Zealand for this originator product when co-prescribed with prednisone as the corticosteroid partner.

11.8. The Committee noted that a number of generic abiraterone acetate products exist and that in April 2022, CTAC considered an application for Yonsa (a generic abiraterone acetate product, used with methylprednisolone 4 mg) for metastatic hormone-naïve and hormone-sensitive prostate cancer. At that time, CTAC recommended it be listed with a high priority and considered that new patients could be initiated on a generic abiraterone acetate product and expect the same level of benefit and risks compared to originator abiraterone acetate. However, the Committee also considered that further evaluation would be required to understand the impact of existing patients changing the steroid component of their hormone duplet therapy.

11.9. The Committee noted that Pharmac had released a Request for Tenders for prednisolone tablets and a possible outcome of this process was that prednisolone tablets would be listed on the Pharmaceutical Schedule as an additional corticosteroid treatment option. The Committee noted that in August 2022, initial advice was sought from the Endocrinology Advisory Committee regarding potential support if prednisolone were to be listed. At that time, the Endocrinology Advisory Committee considered that all prescribers would benefit from information and support if prednisolone tablets were to be funded, given that the majority of prednisolone prescribing would be in primary care and would cover multiple specialities.

Health Need

11.10. The Committee noted that the health need for people with metastatic castration-resistant prostate cancer (mCRPC) requiring abiraterone treatment has been considered by the Committee in previous meetings and did not have any new comments to make regarding this, nor the impact on Māori with prostate cancer.

Health Benefit

11.11. The Committee noted that corticosteroids are used in combination with abiraterone to counteract mineralocorticoid excess (ie nullifying the toxicity resulting from abiraterone's selective blockade of CYP17A1) and are thought to abrogate a molecular escape mechanism to abiraterone (ie suppressing upregulation that results in increased production of androsterone, exposure to androgens and possibly contributing to abiraterone resistance).

11.12. The Committee noted the glucocorticoid and mineralocorticoid potencies of prednisone, prednisolone, methylprednisolone and dexamethasone relative to cortisol. The Committee noted that, as generic abiraterone acetate products cannot use prednisone as a corticosteroid partner without patent violation, most clinical trials investigating generic abiraterone acetate use methylprednisolone and that dexamethasone may be used in trials of patients whose disease has progressed.

11.13. The Committee noted observational evidence that dexamethasone 0.5mg QD counteracted the mineralocorticoid excess from abiraterone acetate by suppressing the adrenocorticotropic hormone (ACTH) and endogenous steroids in 42 patients with mCRPC (Attard et al. J Clin Endocrinol Metab. 2012;97:507-16). Members considered this study also provided biochemical evidence that abiraterone abrogated the molecular escape mechanism, as serum testosterone was reduced after dexamethasone administration.

11.14. The Committee noted evidence from a phase II, randomised, controlled trial investigating the impact of different glucocorticoids, doses and schedules on mineralocorticoid excess in 164 patients with mCRPC (Attard et al. JAMA Oncol. 2019;5:1159-67). Participants received prednisone (5 mg twice daily, 5 mg once daily, or 2.5 mg twice daily) or dexamethasone 0.5 mg once daily. The primary endpoint was no mineralocorticoid excess toxicities (grade ≥1 hypokalaemia or grade ≥2 hypertension) through 24 weeks of treatment; abiraterone acetate with prednisone 5 mg twice daily and dexamethasone 0.5 mg once daily met the prespecified threshold. The Committee considered that the study was of good quality and indicated that the chosen corticosteroid likely did not matter so long as the doses were equivalent, although noted that dexamethasone was the most potent and had the biggest effect in terms of hormone changes, mineralocorticoid excess and glucocorticoid toxicity.

11.15. The Committee noted evidence from a two-period, randomised, crossover, open-label, two-treatment, Phase I study investigating the impact of an alternative steroid on the relative bioavailability and bioequivalence of a novel versus the originator formulation of abiraterone acetate in 37 healthy males (Hussaini et al. Cancer Chemother Pharmacol. 2017;80:479-86). Participants received methylprednisolone 4 mg twice daily or prednisone 5 mg twice daily then on Day 11, subjects given methylprednisolone received a single dose of abiraterone acetate fine particle (AAFP) 500 mg, and subjects given prednisone received a single dose of originator abiraterone acetate (OAA) 1000 mg. After a 2-week steroid washout period, subjects received the alternate treatments in Period 2. The Committee considered that this clinical pharmacology study was well conducted and considered the results indicate that twice-daily methylprednisolone 4 mg or prednisone 5 mg were comparable.

11.16. The Committee noted a systematic review of nine studies investigating a steroid switch after progression on abiraterone plus prednisone in patients with mCRPC (Xiong et al. Urol Oncol. 2021;39:754-63). The Committee considered that this series of retrospective observational cohorts had poor baseline control, where patients transitioned from prednisone or prednisolone on variable progression criteria to dexamethasone. The Committee considered that this showed a consistent 30% or greater decline in PSA (PSA30) and considered this was a sizeable effect, although it was unclear why dexamethasone was chosen rather than another corticosteroid.

11.17. The Committee noted a prospective, single-arm, open-label, phase II pilot study of the prednisone to dexamethasone switch in 26 patients with mCRPC with limited

progression while on treatment with abiraterone plus prednisone for at least 12 weeks (SWITCH study) (Romero-Laorden et al. Br J Cancer. 2018;119:1052-9). The primary endpoint was PSA30 at six weeks which was achieved by just under half of the participants. Members considered this suggests a greater benefit from dexamethasone than simply its potency.

11.18. The Committee also noted the following evidence identified by Pharmac staff:

- Roviello et al. Int J Clin Oncol. 2020;25:240-6
- Hall et al. J Urol, 2021, 206(SUPPL 3), e585-6
- Yang et al. BMC Cancer. 2021;21:919
- McKay et al. Cancer. 2019;125:524-32
- Roviello et al. Med Oncol. 2017;34:166
- Zhou et al. Transl Androl Urol. 2022;11:1189-99
- Fenioux et al. BJU Int. 2019;123:300-6

11.19. The Committee considered that the evidence was of good strength and quality, coming from relatively similar small population cohorts that would be comparable to the New Zealand population. Members considered that there was also some evidence investigating a relatively low dose of corticosteroid with abiraterone acetate which indicated there was no clinically meaningful impact from the lower dose compared to usual doses, although noted that this was investigating a reduction in cardiovascular risk and was supported by observational data only.

11.20. The Committee considered the available evidence indicated that no therapeutic differences would be expected with equivalent corticosteroid doses, that differences in toxicity would be non-significant, and that corticosteroids at equivalent doses could be considered interchangeable in this context. The Committee considered that no clinical concerns were identified in regard to switching either abiraterone acetate or its corticosteroid partner. However, the Committee noted that individuals receiving abiraterone acetate may have been stable on this treatment for up to three years and considered that, while some would be expected to experience disease progression while on long-term abiraterone acetate treatment, some people may be anxious about switching and those who did progress post-switch may attribute progression to the switch. The Committee considered that it would not be appropriate for individuals to return to the abiraterone acetate originator upon disease progression.

11.21. The Committee considered that while it was possible that further evidence might be generated regarding dexamethasone as a corticosteroid partner for abiraterone acetate, no other evidence would be expected to eventuate regarding abiraterone acetate (generic or originator) with other, different corticosteroid partners.

Suitability

11.22. The Committee noted that all corticosteroids that could be partnered with an abiraterone acetate product are oral tablets and therefore considered that there were no differences in terms of suitability that should be considered.

11.23. The Committee considered that there would be no impact for people starting on treatment, who commenced treatment with a generic abiraterone acetate and a different corticosteroid partner (ie not prednisone), and that minimal information or support would be required for these prescriber discussions.

11.24. The Committee considered that individuals switching to a funded generic abiraterone acetate with a different corticosteroid partner (ie not prednisone) would benefit from prescriber education regarding the evidence for corticosteroid dose equivalence and reassurance that these dose differences would not be expected to impact on the efficacy or toxicity of abiraterone acetate, in addition to information to support these prescriber discussions. The Committee considered that this may be additionally helpful for prescribers who may be less familiar with prescribing steroid medications.

11.25. The Committee considered that Pharmac could also investigate supporting the implementation of such a switch with pharmacist alerts to review prescriptions for abiraterone acetate and corticosteroids.

Costs and Savings

11.26. The Committee noted that some clinicians would want to switch people to dexamethasone upon PSA progression and considered that, while not strictly permitted according to the current Special Authority criteria, where this occurs it could extend overall time on abiraterone acetate for a proportion of people.

Special Authority criteria

11.27. The Committee considered that it would be appropriate for Pharmac to specify a corticosteroid partner for abiraterone acetate in the Special Authority criteria, and/or consider funding a combination pack of generic abiraterone acetate and corticosteroid partner.

General

11.28. The Committee considered that it would be appropriate for Pharmac to progress a competitive process for abiraterone acetate that could result in the funding of a generic abiraterone acetate with a different corticosteroid (ie not prednisone) for all patients currently receiving or initiating funded treatment with abiraterone acetate. The Committee considered that prescribers would likely be comfortable prescribing any corticosteroid partner other than prednisone to accompany generic abiraterone acetate.

11.29. The Committee considered that it would like to review its recommendations for proposals for abiraterone acetate based upon any future price changes, given that the anticipated cost was a factor in some of the Committee's previous recommendations for this medicine.

12. Ripretinib for people with advanced metastatic or unresectable gastrointestinal stromal tumours (GIST) who have experienced disease progression following treatment with imatinib and sunitinib

Application

12.1. The Committee reviewed the application from Specialised Therapeutics Limited for ripretinib for people with advanced metastatic or unresectable gastrointestinal stromal tumours (GIST) that have experienced disease progression following treatment with imatinib and sunitinib.

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 ripretinib for people with advanced metastatic or unresectable gastrointestinal stromal tumours (GIST) that have experienced disease progression following treatment with imatinib and sunitinib be listed with a **high priority** within the context of treatments of malignancy, subject to the following Special Authority criteria:

Initial application – (GIST) only from any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months for applications meeting the following criteria:
All of the following:
1. The patient has unresectable or metastatic malignant gastrointestinal stromal tumour (GIST); and
2. Either:
    2.1. The patient's disease has progressed following treatment with imatinib and sunitinib; or
    2.2. The patient has experienced intolerable side effects or toxicity from imatinib and sunitinib which have been treatment-limiting.

Renewal – (GIST) only from any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:
One of the following:
1. The patient has had a complete response (disappearance of all lesions and no new lesions), as per Choi's modified CT response evaluation criteria (J Clin Oncol, 2007, 25:1753-1759); or
2. The patient has had a partial response (a decrease in size of 10% or more or decrease in tumour density in Hounsfield Units (HU) of 15% or more on CT and no new lesions and no obvious progression of non-measurable disease), as per Choi's modified CT response evaluation criteria; or
3. The patient has stable disease as determined by Choi's modified CT response evaluation criteria (eg does not meet criteria the two above) and does not have progressive disease and no symptomatic deterioration attributed to tumour progression; or
4. The patient has experienced their first progression of disease, as per Choi's modified CT response evaluation criteria, since initiating ripretinib treatment for GIST and has ongoing clinical benefit.

12.4. In making this recommendation, the Committee considered:

- The high health need for people with advanced or metastatic unresectable GIST who have progressed following treatment with imatinib and sunitinib, particularly regarding the decreased health-related quality of life and poor health outcomes experienced by individuals within this group, and the severe impact on family/whānau.

- The good quality and strength of evidence demonstrating that ripretinib provides a health benefit in those with advanced or metastatic unresectable GIST with a manageable toxicity profile.

- The suitability of ripretinib as an oral formulation with a straightforward dosing regimen that can be administered in a community setting.

Discussion

Māori Impact

12.5. The Committee discussed the impact of funding ripretinib for the treatment of advanced or metastatic unresectable gastrointestinal stromal tumours (GIST) that have progressed following treatment with imatinib and sunitinib on Māori health areas of focus and Māori health outcomes. The Committee noted that the number of people with GIST in New Zealand is small and there is consequently limited evidence in this area. The Committee noted that no evidence was identified regarding the impact of advanced GIST on Māori health outcomes. The Committee

considered that Māori are more likely to be diagnosed with more advanced disease across all cancer types, and that this is likely to also apply to those with GIST.

Health Need

12.6. The Committee noted that GISTs are rare and account for 1% to 2% of gastrointestinal neoplasms. The Committee noted that GISTs that arise from the bowel wall typically present as subepithelial neoplasms in the stomach and small intestine; however, they can also arise in any portion of the gastrointestinal tract and, occasionally, the omentum, mesentery, and peritoneum (Morgan et al. UpToDate. September 2022). The Committee noted that 85% of people with GIST have mutually exclusive mutations in receptor tyrosine kinase (KIT; 75 to 20%) and platelet-derived growth factor receptor alpha (PDGFRA; 5 to 10%).

12.7. The Committee noted that the incidence of soft tissue sarcomas from the New Zealand Cancer Registry for the years 2015 to 2018 is approximately 120 patients annually (New Zealand Cancer Registry Data for 2015, 2016, 2017, and 2018). The Committee noted that only a small proportion of these are GIST and only a proportion of these would be considered high risk, metastatic, and inoperable tumours appropriate for pharmacological treatment (see submission documents).

12.8. The Committee noted that the only New Zealand publication on GIST documents 93 patients diagnosed and treated for GIST in Christchurch Hospital between 1 January 2000 and 31 December 2010 (an 11-year period). The Committee noted that: 50 patients were women; the median age of diagnosis was 69 (interquartile range [IQR] 59 to 76) years; and 51 tumours were located in the stomach, 27 in the small bowel, six in the colon, three in the oesophagus, one in the rectum and five were extra-gastrointestinal (Siu et al. ANZ J Surg. 2016;86:162-6). The Committee also noted a systematic review of literature (2000-2014) on the epidemiology of GIST noted that most studies reported incidence at 10-15 per million per year (equivalent to 50-75 people annually in New Zealand). The Committee noted that the range of incidence was 4.2 to 22 cases per million, which would equate to 20-100 cases in New Zealand annually (Søreide et al. Cancer Epidemiol. 2016;40:39-46).

12.9. The Committee considered that there is an unmet health need for those with advanced or metastatic unresectable GIST. The Committee noted that advanced GIST is associated with pain, nausea, GI bleeding, abdominal bloating, and fatigue. The Committee noted that larger tumours may cause obstruction of the gastrointestinal lumen by endophytic growth or compression of the GIT from exophytic growth leading to dysphagia, obstructive jaundice, or constipation, depending on the location of the mass (Parab et al. J Gastrointest Oncol. 2019;10:144-54).

12.10. The Committee noted that people with GIST who have trialled imatinib and sunitinib are treatment experienced and have metastatic and inoperable tumours that impact on their everyday life. The Committee noted that their life expectancy is short (a matter of months) and they have no further treatment available to them, other than best supportive care (ie palliative care), including pain and symptom management. The Committee noted that in Sui et al, the 5-year overall survival (OS) and disease-free survival (DFS) for the entire study population was 69% and 64%, respectively. The Committee noted that the 5-year DFS was higher for all patients who have localised disease when compared with those who have metastatic disease (76% versus 28%, *P*=0.001) (Siu et al. ANZ J Surg. 2016;86:162-6).

12.11. The Committee noted that people with advanced GIST are functionally impaired, with 19% having a baseline ECOG score of 2 or 3 (Reddy et al. J Clin Pharm Ther. 2007;32:557-65; Demetri et al. N Engl J Med. 2002;15:347:472-80). The Committee noted a study found that 39% of those with GIST endure pain at least a few days a week, leading to a disruption in activities of daily living in over half of patients, and that those who regularly suffer from pain are more likely to become upset or anxious (Wiener et al. Support Care Cancer. 2012;20;1343-9).

12.12. The Committee noted that in New Zealand, people with advanced or metastatic GIST would receive imatinib as first line treatment, followed subsequently by sunitinib (both currently funded under Special Authority criteria). The Committee noted that nearly all patients will become resistant to imatinib, with 40% to 50% of patients developing resistance and experiencing disease progression within 2 years, largely driven by secondary receptor tyrosine kinase (KIT) mutations. The Committee noted that once a patient progresses on sunitinib, best supportive care is provided, and that conventional chemotherapy and radiotherapy are not effective in this population with advanced disease. The Committee noted that regorafenib is also approved by Medsafe for the treatment of advanced unresectable or metastatic GIST but is not commercially available in New Zealand, nor has Pharmac received a funding application for this medicine.

12.13. The Committee noted a cross-sectional study reporting that caregivers of those with GIST who had been treated with TKIs experience high levels of burden (10%) and distress (23%). The Committee noted that caregivers with high levels of burden perceived significantly lower mental health, less vitality, lower general health, and high levels of distress. The Committee noted that caregivers with high levels of distress perceived significantly more burden, lower social functioning, more role physical and emotional problems, lower mental health, less vitality, and lower general health (Langenberg et al. Acta Oncol. 2019;58:191-9).

12.14. The Committee noted that in the consumer submissions to the Australian Pharmaceutical Benefits Advisory Committee (PBAC), people with GIST described exhaustion and frustration with their disease, as well as frustration with a lack of available treatment options for this rare cancer.

12.15. The Committee noted that this funding application aligns with the Government health priorities, noting that cancer is considered a priority condition.

Health Benefit

12.16. The Committee noted that ripretinib is a KIT inhibitor designed to inhibit the KIT proto-oncogene receptor tyrosine kinase and PDGFRA and was developed for the treatment of advanced GIST. The Committee noted that ripretinib is not currently Medsafe approved, and that the supplier has submitted an application to Medsafe for the requested indication. The Committee noted that the supplier's proposed datasheet states that the recommended dosage of ripretinib is 150 mg (three 50 mg tablets) orally once daily with or without food until disease progression or unacceptable toxicity.

12.17. The Committee noted that the key evidence for ripretinib for advanced GIST comes from the INVICTUS trial (NCT03353753), a double-blind, randomised, placebo-controlled, phase III study. The Committee noted that this trial evaluated the efficacy of 150 mg ripretinib once daily in 129 patients with advanced GIST with progression on at least imatinib, sunitinib, and regorafenib or documented

intolerance to any of these treatments despite dose modifications. The Committee noted the following publications reported on this trial:

12.17.1. The Committee noted that, after a median follow up of 6.3 months for the ripretinib group (inter-quartile range [IQR] 3.2 to 8.2) and 1.6 months (IQR 1.1 to 2.7) for the placebo group, 51 patients in the ripretinib group and 37 in the placebo group had progression free survival (PFS) events. The Committee noted that in the double-blind period, median PFS was 6.3 months (95% confidence interval [CI] 4.6 to 6.9) with ripretinib compared with 1.0 months (0.9 to 1.7) with placebo (hazard ratio [HR] 0.15, 95% CI 0.09 to 0.25; *P*<0.0001). The Committee noted that PFS at 6 months were estimated to be 51% (39.4 to 61.4) for ripretinib and 3.2% (0.2 to 13.8) for placebo. The Committee noted that median overall survival (OS) was 15.1 months (95% CI 12.3 to 15.1) in the ripretinib group and 6.6 months (4.1 to 11.6) in the placebo group (HR 0.36, 95% CI 0.21 to 0.62), inclusive of the double-blind and open-label periods, however that this could not be formally tested for statistical significance due to hierarchical testing. The most common adverse events reported in the ripretinib group (n=85) were alopecia, fatigue, myalgia, nausea, diarrhoea, and palmar-plantar erythrodysaethesia, and 4 patients in this group required treatment discontinuation due to adverse effects (Blay et al. Lancet Oncol. 2020;21:923-34).

12.17.2. The Committee noted the results of subgroup analysis where sub-groups were determined by KIT/PDGFRA mutations and correlation of clinical outcomes and KIT/PDGFRA mutational status was assessed. The Committee noted that the most common primary mutation subgroup detected by combined tissue and liquid biopsies were in KIT exon 11 (ripretinib, 61.2%; placebo, 77.3%) and KIT exon 9 (ripretinib, 18.8%; placebo, 15.9%). The Committee noted that patients receiving ripretinib demonstrated PFS benefit versus placebo regardless of mutation status (HR 0.16) and in all assessed subgroups in Kaplan–Meier PFS analysis (exon 11, *P*<0.0001; exon 9, *P*=0.0023; exon 13, *P*<0.0001; exon 17, *P*<0.0001). The Committee noted that, among patients with wild-type KIT/PDGFRA by tumour tissue, PFS ranged from 2 to 23 months for ripretinib versus 0.9 to 10.1 months for placebo (Bauer et al. Clin Cancer Res. 2021;27:6333-42).

12.17.3. The Committee noted the results of a subgroup analysis of the patients who were randomised to ripretinib 150 mg once daily in the INVICTUS trial who underwent intra-patient dose escalation (IPDE) to ripretinib 150 mg twice daily following progressive disease (PD). The Committee noted that among the ripretinib IPDE patients, PFS1 was the time from randomisation until PD; PFS2 was the time from the first dose of ripretinib 150 mg twice daily to PD or death. The Committee noted that among 43 ripretinib patients, median PFS1 was 4.6 months (95% CI 2.7 to 6.4) and median PFS2 was 3.7 months (95% CI 3.1 to 5.3). The Committee noted that the median OS was 18.4 months (95% CI, 14.5 to not estimable) in patients randomised to ripretinib 150 mg one daily with PD and receiving IPDE to 150 mg twice daily (n=43) and 14.2 months (95% CI 7.2 to not estimable) in those randomised to ripretinib 150 mg once with PD and not receiving IPDE (n =22) (HR, 0.74; 95% CI 0.37 to 1.49). The Committee noted that among the intention-to-treat population of INVICTUS, median OS was 18.2 months (95% CI, 13.1 to not estimable) in the ripretinib group (n=85) versus 6.3 months (95% CI 4.1 to 10 months) in the placebo group (n=44) (HR 0.42; 95% CI 0.27 to 0.67) (Zalcberg et al. Oncologist. 2021;26:e2053-60).

12.18. The Committee was made aware of the INTRIGUE trial (NCT03673501), and international, multi-centre, open label, randomised, phase III study. The Committee noted this trial compared the efficacy of ripretinib 150 mg once daily (n=226) and sunitinib 40 mg once daily (n=227) in 453 patients with advanced GIST who had progressed on or experienced intolerances to imatinib. The Committee noted that median PFS for ripretinib and sunitinib (*KIT* exon 11 intention to treat [ITT]) was 8.3 and 7.0 months, respectively (HR 0.88; 95% CI 0.66 to 1.16; *P*=0.36); median PFS (ITT) was 8.0 and 8.3 months, respectively (HR 1.05; 95% CI 0.82 to 1.33; nominal *P*=0.72), and that neither of these results were statistically significant. The Committee noted that there was a higher rate of adverse events leading to dose reduction and study discontinuation in the sunitinib group (Bauer et al. J Clin Oncol. 2022 [online ahead of print]).

12.19. The Committee was made aware of an updated review of the treatment landscape for advanced GIST. The Committee noted that this publication reported the overall response rates (ORR) for the following treatments: imatinib 45%, avapritinib 93% (95% CI 77 to 99), sunitinib 7%, regorafenib 4.5%, and ripretinib 9.4% (95% CI 4.2 to 17.7). The Committee also noted the median PFS across treatments: imatinib 18 months (95% CI 16 to 21), avapritinib not estimable (NE), sunitinib 5.5 months (95% CI 2.6 to 6.5), regorafenib 4.8 months (95% CI 4.1 to 5.8), and ripretinib 6.3 (95% CI 4.6 to 6.9). The Committee noted that the median OS was 55 (95% CI 47 to 62) months for imatinib and 15.1 (95% CI 12.3 to 15.1) months for ripretinib (Patel, Reichardt. Cancer. 2021: 127:2187-2195).

12.20. The Committee was made aware of a phase I study of ripretinib in 258 patients with advanced GIST, which included a dose-escalation phase (n=68) and subsequent expansion phase at the recommended phase II dose. The Committee noted that the median PFS ranged from 5.5 months (fourth line or greater) to 10.7 months (second line). The Committee noted that the ORR was 11.3% (n=16/142) ranging from 7.2% (n=6/83; fourth line or greater) to 19.4% (n=6/31; second line). The Committee noted that the median time (range) to response among responders was 3.7 (1.7-13.6) months, and the median duration of response was 18.4 (95% CI, 11.1 to NE) months in the 16 responders receiving ripretinib 150 mg once daily, with nine patients continuing to respond as of the data cut-off (Janku et al. J Clin Oncol. 2020; 38:3294).

12.21. The Committee considered that the evidence for the health benefit of ripretinib is of good quality and strength and noted the limited data in this area given the rarity of the disease. The Committee considered that the evidence from the INVICTUS trial investigates the use of ripretinib in the fourth line, whereas this funding application proposes use of ripretinib in the third line, and that therefore a longer PFS would be expected if ripretinib were to be used in an earlier line. The Committee considered that the available evidence supports the use of ripretinib dose escalation after disease progression, and there is limited evidence on how outcomes may change if ripretinib was not permitted to be used after the first sign of disease progression.

12.22. The Committee noted that OS in the placebo arm of the INVICTUS trial was confounded by crossover from the ripretinib arm and considered that there is limited follow-up data for this study to further investigate this. The Committee considered that this resulted in the benefit of ripretinib being underestimated in the reported outcomes, and the that the OS benefit is likely to be greater than that observed. The Committee also noted that among those randomised to placebo, median OS was 11.6 months among those who crossed over to ripretinib upon progression, compared to 1.8 months for those who did not cross over. The Committee considered that those who did not cross over were likely a selected subgroup of

individuals for whom ripretinib was not suitable, and that this does not represent outcomes for all patients treated with placebo. The Committee considered that median OS with placebo was likely to be somewhere between the OS of those who did not cross over (1.8 months) and the OS of the intention-to-treat population (6.3 months).

12.23. The Committee considered that the evidence demonstrates that ripretinib provides a health benefit in terms of PFS accompanied by improved overall wellbeing. The Committee considered that the quality-of-life improvements observed in patients would have a flow on impact to whānau and the community. The Committee considered that ripretinib has relatively few side effects requiring hospital admission.

Suitability

12.24. The Committee noted that ripretinib is an oral medication that is administered once daily at approximately the same time each day. The Committee noted that tablets should be swallowed whole with water, which may be challenging for those who have difficulty with swallowing medicines. The Committee noted that the oral formulation and straightforward dosing regimen may otherwise support adherence. The Committee noted that, as it can be self-administered by the individual or a caregiver in the community, the burden of treatment delivery and need for repeated attendance at a hospital or outpatient facility would be minimised.

Cost and Savings

12.25. The Committee considered that, if ripretinib were to be funded, approximately 90% of those who initiate sunitinib would require ripretinib due to either disease progression of intolerable side effects. The Committee considered that individuals receiving ripretinib dose escalation upon disease progression would need to be of good performance status and that it is unlikely individuals would continue the escalated dose beyond second progression. The Committee noted there was little information about whether any patients in INVICTUS continued receiving the 150 mg daily dose after first progression.

12.26. The Committee considered that funding ripretinib would result in the eligible population living longer, thereby increasing clinician follow up and imaging appointments to monitor disease activities. The Committee considered that ripretinib would also likely delay time to hospitalisation for those with advanced GIST due to the associated PFS benefit and quality of life benefit. The Committee noted that in the INVICTUS trial, patients were assessed fortnightly initially and then once every four weeks and considered this to be an appropriate estimate of health resource utilisation for people with advanced GIST. The Committee considered that those eligible to receive ripretinib will also require supportive care medications for the management of disease- or treatment-related symptoms (eg diarrhoea and nausea).

12.27. The Committee noted the Pharmac estimate of 13 people per year who had progressed following prior sunitinib. The Committee considered that there were five individuals managed in Auckland alone over the last three months who would meet the proposed Special Authority criteria, suggesting that the treatment group may be larger than this. The Committee also noted that of the group managed in Auckland, two were Māori and two were of Pacific ethnicity, suggesting a disproportionate impact across ethnicities. The Committee considered Pharmac should further interrogate the data to refine these numbers.

Summary for Assessment

12.28. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for ripretinib if it were to be funded in New Zealand for the treatment of advanced or metastatic unresectable gastrointestinal stromal tumours (GIST) that have progressed following treatment with imatinib and sunitinib. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with advanced GIST who have either experienced disease progression or intolerable side effects from both imatinib and sunitinib
Intervention	Ripretinib, at a dose of 150 mg once daily until disease progression Individuals may then escalate the dose to 150 mg twice daily upon disease progression, on which they may continue until second progression. In the INVICTUS trial, 66% of those who progressed on ripretinib received 150 mg twice daily upon disease progression.
Comparator(s) (NZ context)	Best supportive care
Outcome(s)	Longer progression-free survival (PFS) Likely longer overall survival • Magnitude slightly uncertain owing to the crossover from the placebo arm in INVICTUS • OS in the comparator arm likely to be between the intention-to-treat OS, and the OS of those who did not cross over from placebo to ripretinib PFS and OS in a third line setting likely to be higher than that observed in INVICTUS, where patients were treated fourth line
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

13. Commercial options for lenalidomide and pomalidomide

Discussion

13.1. The Advisory Committee noted that Pharmac was seeking advice regarding a potential competitive procurement process for lenalidomide and pomalidomide.

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

Recommendation

13.3. The Advisory Committee supported a competitive process for lenalidomide resulting in principal supply status for a single supplier of lenalidomide.

Discussion

Lenalidomide

13.4. The Committee noted that lenalidomide has been funded in combination with dexamethasone as third line treatment for people with multiple myeloma, and as second line treatment for those that experience grade 3 or 4 neuropathy since 2014. The Committee noted that access was widened to lenalidomide as maintenance therapy in April 2020 for people with myeloma after receipt of an autologous stem cell transplant (SCT). The Committee noted that the first line use of lenalidomide for individuals eligible for a transplant and ineligible for a transplant has been ranked as an option for investment.

13.5. The Committee noted that approximately 20% of those who receive lenalidomide in the relapsed or refractory setting, receive it in the second line setting and considered that this proportion may be higher than the proportion who would likely experience grade 3 or 4 neuropathy.

13.6. The Committee noted that those individuals who access lenalidomide as part of first line treatment do so after autologous stem cell transplant. The Committee noted that these patients are younger and fitter than patients who are not eligible for a transplant. The Committee noted that patients who are older and less fit need to wait until they require third line treatment in order to be eligible to access lenalidomide. Therefore, the Committee considered that the greatest inequity regarding early access to lenalidomide is a person's age at diagnosis and uptake of autologous-SCT. The Committee noted that Māori are diagnosed at an earlier age, yet receipt of autologous-SCT is lower for Māori than non-Māori. The Committee considered that despite the reduced receipt of autologous-SCT, the younger age at diagnosis for Māori is dominant and this results in Māori receiving lenalidomide at a younger age than non-Māori.

13.7. The Committee noted a European study that reported that while nearly all patients with myeloma received first line treatment, only 38% of patients in the study received third line treatment (Yong et al. Br J Haematol. 2016; 175(2):252-264), and that the efficacy of lenalidomide reduces as exposure to prior therapy increases. The Committee noted that for those over 75 years of age, the likelihood of receiving third line treatment is substantially lower than those under 75 years of age. The Committee noted parallels with this for Māori with myeloma, in that fewer Māori receive autologous-SCT than non-Māori and therefore, fewer are eligible for treatment with lenalidomide as first line maintenance therapy post autologous-SCT.

13.8. The Committee noted that there are many generic lenalidomide products that have received, or, are in the process of seeking, Medsafe approval. The Committee noted a study assessing the efficacy and safety of generic lenalidomide (Bolaman et al. Turk J Haematol. 2021;38(1):41-48). The Committee considered that any assessment of the bioequivalence and safety of generic lenalidomide products is considered by Medsafe.

13.9. The Committee noted the extensive experience of Pharmac and New Zealand for generic brand changes, for both malignant and non-malignant diseases. The Committee considered any potential brand change for lenalidomide would be straightforward. However, the Committee noted the unique arrangements for the management of teratogenicity of immunomodulatory drugs (thalidomide, lenalidomide etc.). The Committee noted that this has resulted in a complex and time intensive risk management programme to manage this risk, which includes registration of pharmacies, doctors and individuals receiving thalidomide and

lenalidomide to enable the safe use of these agents. The Committee noted that there are many other teratogenic pharmaceuticals, which do not have stringent risk management programmes in place, however considered that this unique management of risk for this class of drugs would continue to be required by Medsafe. The Committee considered that the associated risk management programme would need to be considered as part of the proposal put forth by suppliers for access to lenalidomide, should there brand change for this pharmaceutical.

13.10. The Committee noted that this risk management programme does currently have an impact on access to lenalidomide for the currently funded population, due to the maximum dispensing quantities for lenalidomide, and that not every pharmacy is registered with the programme and therefore cannot dispense lenalidomide.

13.11. The Committee considered that should there be a brand change for this market, there would need to be:

13.11.1. clear communications to those on lenalidomide and healthcare professionals in relation to the change, that they would be switched at their next appointment and that the new brand is equivalent to the old brand.

13.11.2. clear communications regarding any transition to a new risk management programme, and that this would need to be well implemented. The Committee considered that anyone on lenalidomide would need to be reconsented onto the new risk management programme and that this may be time intensive for clinicians, pharmacists and individuals taking lenalidomide.

13.11.3. as few risk management programmes available for registration as possible, to limit confusion and the administrative requirements. The Committee noted that even if there were a brand change, it would be likely that there would remain a need to retain the innovator lenalidomide risk management programme, should an individual need to transition back to the innovator lenalidomide.

13.12. The Committee considered that given the complexity of the change, due to the necessity for a risk management programme, it may not be appropriate to include lenalidomide in the annual Invitation to Tender given the additional implementation support that may be required to support any potential brand change.

13.13. The Committee considered that there would be no adverse impacts for Māori or Pacific peoples should there be a brand change for this market. The Committee considered that a competitive process could result in the funding of lenalidomide in the first line setting and that if this were to occur, there would be substantial benefits for all, including Māori and Pacific people with myeloma, in that they would be able to receive an oral regimen in the front line setting, noting that fewer Māori and Pacific people are currently eligible for first line maintenance treatment with lenalidomide, due to the reduced rates of autologous -SCT in these populations in New Zealand.

13.14. The Committee noted that on average, people who receive lenalidomide under the current access criteria remain on treatment for approximately 2-3 years. The Committee noted that the earlier in the treatment paradigm a person receives lenalidomide, the longer they would be expected to remain on treatment. The Committee considered that given this trend, if access were widened to people earlier in the treatment paradigm, it would be likely that they would remain on

treatment for longer. Given this, the Committee considered that it would be beneficial to limit the number of brand changes for this group and therefore, there would be benefit in a longer principal supply period for this agent.

13.15. The Committee considered that there are no pre-identifiable populations for whom a brand change would pose a specific risk. The Committee considered that all individuals with multiple myeloma would eventually experience disease progression on lenalidomide and that this would not be attributable to a brand change. The Committee considered that people with multiple myeloma do not relapse quickly, but rather that relapse occurs over a period of time. However, the Committee acknowledged that there may be a small group of individuals who experience hypersensitivity reactions to the generic lenalidomide. The Committee considered that it would be appropriate for Pharmac to manage a return to innovator lenalidomide on a case-by-case basis via Pharmac's Exceptional Circumstances Framework.

13.16. The Committee considered that if a brand change were to occur for this market and it was accompanied by greater access to lenalidomide, this would significantly assist the palatability of any change for this market. The Committee considered that beyond the previously considered indications, access to lenalidomide could be widened to include:

13.16.1. Combination treatment with other unfunded treatments for myeloma (daratumumab, carfilzomib, ixazomib) when disease relapse occurs, similar to that of bortezomib and thalidomide.

13.16.2. Myelodysplastic syndrome with a del5q mutation

13.16.3. In combination with rituximab for follicular lymphoma

13.17. The Committee considered that there would be significant benefit in retaining the availability of the currently funded strengths and pack sizes, should there be a change to a generic lenalidomide.

Pomalidomide

13.18. The Committee noted that pomalidomide is available in the first line setting in other jurisdictions, as it has greater activity than both lenalidomide and thalidomide. The Committee noted that both it and PTAC had previously considered pomalidomide for the 2nd line, 3rd line and 4th line therapy.

13.19. The Committee considered that there would be similar considerations for pomalidomide as lenalidomide, although noted that there would not need to be any consideration regarding brand changing as it is not currently funded. The Committee considered that it would be beneficial to fund all strengths as a result of a potential competitive process, however noted that only the 3 mg and 4 mg strengths are funded in Australia, and considered this to be the minimum requirement. The Committee considered that there would be a benefit in having the same supplier of lenalidomide and pomalidomide as this would mean that there would be a single risk management programme available, which this would simplify access for those on lenalidomide, pharmacists and clinicians.

13.20. The Committee noted that due to the similarity in mechanism of action for lenalidomide and pomalidomide, there would be a group of individuals for whom pomalidomide may not be suitable after lenalidomide exposure (eg those who had experienced myelosuppression), and considered that even with the funding of

pomalidomide, there would remain an unmet need for novel agents (daratumumab and carfilzomib.

14. Bortezomib for the treatment of Waldenström macroglobulinemia

Application

14.1. The Advisory Committee reviewed bortezomib for the treatment of Waldenström macroglobulinemia (WM), based on its previous considerations at the November 2021 Cancer Treatment Subcommittee of PTAC (CaTSoP) meeting.

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

Recommendation

14.3. The Advisory Committee **recommended** that bortezomib in the treatment of Waldenström macroglobulin be listed with a **medium priority** within the context of treatments of malignancy, subject to the following Special Authority criteria:

> **BORTEZOMIB**
> **Initial application – Waldenström Macroglobulinaemia (Lymphoplasmacytic Lymphoma)**
> Applications from any relevant practitioner. Approvals valid for 12 months.
> **Prerequisites** (tick boxes where appropriate):
> 1. The patient has Waldenström Macroglobulinaemia/Lymphoplasmacytic Lymphoma requiring treatment; and
> 2. The patient's condition is bortezomib treatment naïve.
>
> **Renewal application**
> Applications from any relevant practitioner. Approvals valid for 12 months.
> **Prerequisites** (tick boxes where appropriate)
> 1. No evidence of clinical disease progression and
> 2. The treatment remains appropriate, and the patient is benefiting from treatment

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

- The high health need for people with untreated WM where bendamustine-rituximab (BR) is not suitable, and for people with relapsed WM.
- The evidence for the use of bortezomib in WM is of poor quality, especially in the relapsed/refractory setting, with no head-to-head data comparing bortezomib-dexamethasone-rituximab (BDR) with other common regimens (dexamethasone-rituximab-cyclophosphamide (DRC) and rituximab-cyclophosphamide-vincristine-prednisone (R-CVP)).
- The suitability of bortezomib as a widely used subcutaneous injection that can be administered in both urban and rural outpatient settings.
- The cost of bortezomib compared to other funded and unfunded treatments for WM

Discussion

Māori Impact

14.5. The Committee discussed the impact of funding bortezomib for the treatment of WM on Māori health areas of focus and Māori health outcomes. The Committee noted that no evidence was identified in this area.

Background

14.6. The Committee noted that an application for ibrutinib for the treatment of WM was assessed at the November 2021 CaTSoP meeting and two recommendations were made. The Committee noted that CaTSoP recommended that ibrutinib for the treatment of first line WM be listed with a low priority, and that ibrutinib for the treatment of patients with relapsed/refractory WM be listed with a medium priority.

14.7. The Committee noted that, during this meeting, CaTSoP also noted that bortezomib in combination with dexamethasone +/- rituximab has also been shown to be efficacious in patients with WM. The Subcommittee noted that bortezomib is not currently funded for people with WM and requested to review bortezomib for the treatment of people with WM at a future meeting.

Health Need

14.8. The Committee noted that WM is an incurable lymphoproliferative B-cell disorder characterised by infiltration of lymphoplasmacytic cells into the bone marrow and immunoglobulin M (IgM) monoclonal gammopathy (Ghobrial. Hematology Am Soc Hematol Educ Program. 2012:586-94; Orphanet. Waldenström macroglobulinemia. 2012). The Committee noted that WM is a progressive, incurable disease that results in reduced function and quality of life, leading to early death.

14.9. The Committee noted that WM is a rare condition, making up approximately 2% of all blood cancers. The Committee noted that the estimated incidence is four persons per million per year in Europe, classifying it as an orphan disease (Orphanet, 2016). The Committee noted it is more common in men than women, and predominantly diagnosed in older people, with a median age at diagnosis of 68 years (Leukaemia Foundation Australia 2021). The Committee considered that at diagnosis treatment is not usually indicated, and that the median time from diagnosis to needing treatment is 5 to 10 years (Kyle et al. Blood. 2012;119:4462-6). The Committee noted that there are approximately 20 to 50 cases in New Zealand per year. The Committee noted that in the funding application received for ibrutinib for treatment of WM, the supplier (Janssen) estimated that approximately 12 people are diagnosed with relapsed/refractory WM per year in New Zealand. The Committee noted that when this application was discussed at the November 2021 CaTSoP Subcommittee meeting, this figure was considered an underestimate, and that actual numbers in New Zealand could be double that estimated by the supplier.

14.10. The Committee noted that symptoms of WM develop slowly and may initially include fatigue, weakness, and weight loss. The Committee noted that, as the disease progresses, several morbidities may arise and impact an affected person's ability to carry out daily activities. The Committee noted that this is particularly debilitating in the elderly population disproportionately affected by WM, who are often affected by comorbidities, limited mobility, and a reduced capacity to tolerate the adverse effects of chemotherapy (Orphanet. 2012; Morel et al. Blood. 2009;113:4163-70).

14.11. The Committee noted that, in the November 2021 CaTSoP meeting, the Subcommittee considered the treatment options (rituximab in combination with chemotherapy) to be effective for people with good performance status living with WM and therefore the health need for this treatment naïve group was comparatively low. The Committee noted that at this time, the Subcommittee considered that the health need for those living with WM is greater for those in which rituximab in combination with chemotherapy is not suitable (eg due to their frailty or comorbidities). The Committee also noted that the Subcommittee considered the

heath need to also be greater for those who have relapsed after, or are refractory to a prior line of treatment, due to the limited treatment options and shorter progression free survival (PFS) in later lines of treatment. The Committee considered that those who relapse will be older and therefore less likely to be treated with BR again, and that Bruton tyrosine kinase (BTK) inhibitors are not funded and therefore not an option for these individuals in New Zealand.

14.12. The Committee noted that in Kastritis et al the WM death rate was 32% and the WM unrelated death rate was 11.5% (Kastritis et al. Haematologica. 2015;100:e446-9). The Committee considered that as WM is a disease occurring predominantly in elderly individuals and that not all individuals with WM would die from this disease.

14.13. The Committee noted that the currently funded treatments for WM include BR as a preferred option, or DRC or rituximab monotherapy in those with comorbidities or low tumour burden. The Committee considered that, in the first line setting, most individuals with good performance status would receive BR for WM. The Committee considered that that BR would be suitable in <10% of people in the second line setting in New Zealand. The Committee considered that for those in which BR is not suitable in the second line setting, R-CVP, rituximab monotherapy, chlorambucil, or DRC would be used instead. It was noted that at the November 2021 meeting, the Committee considered that individuals with relapsed/refractory WM can be retreated with the previous chemotherapy regimen (if this was effective in the previous line), an alternative chemotherapy regimen, or rituximab monotherapy. The Committee noted that CaTSoP considered that efficacy of treatment and PFS with each successive line of treatment would be expected to diminish.

14.14. The Committee noted that treatment with the agents above has been associated with short periods of remission, frequent relapse, and relatively short PFS (Treon et al. Hematol Oncol Clin North Am. 2014;28:945-70; Dimopoulos et al. J Clin Oncol. 2005;23:1564-77). The Committee noted that, in the first line setting, the median PFS is 69.5 months (95% CI 26.1 to not reached) for BR treatment (Rummel et al. Lancet. 2013;381:1203-1210), 34 months (95% CI 23 to not reached) for DRC treatment (Kastritis et al. Blood. 2015;126:1392-1394), and 27.1 months (95% CI 21.0 to 32.1) for chlorambucil (Leblond et al. J Clin Oncol. 2013;31:301-7). The Committee noted that, in the relapsed/refractory setting, the median PFS is 35 months (95% CI 15 to 51) for DRC treatment (Paludo et al. BJH. 2017;179:98-105). The Committee noted that the median PFS is 20.3 months for 8 cycles of rituximab monotherapy, which includes both those who were treatment naïve and relapsed/refractory (Dimopoulos et al. N Engl J Med. 2018;378:2399-2410).

14.15. The Committee noted that bortezomib-containing regimens are listed as a treatment option for both previously untreated and relapsed/refractory people with WM in the European Society for Medical Oncology (ESMO) 2018 Guidelines and National Comprehensive Cancer Network Guidelines. The Committee noted that BDR is also listed as an upfront option for treatment naive WM patients in International Waldenström Working Group (IWWG) and the Australian WM 2022 Guideline. The Committee noted that internationally there is a preference in the relapsed/refractory setting for BTK inhibitors due to their availability, and that BDR should only be considered if BTK inhibitors are contraindicated (IWWG) or if a rapid reduction in IgM is required (Australian WM 2022 Guideline).

14.16. The Committee noted that people with WM living in rural areas are more likely to experience difficulty in accessing services including specialist visits, supportive care, and current treatments for WM that are required to be administered in a hospital or outpatient setting. The Committee noted that elderly people with WM are

also more likely to have poorer outcomes due to their increased frailty, comorbidities, and susceptibility to developing adverse reactions to treatment such as chemotherapy, thereby highlighting the unmet need for an oral treatment option such as a BTK inhibitor (Morel et al. Blood. 2009;113:4163-70).

Health Benefit

14.17. The Committee noted that bortezomib is a proteasome inhibitor and that it is not currently Medsafe approved for treatment of WM.

14.18. The Committee noted that the ESMO Guidelines recommend bortezomib is given at a dose of 1.5 mg/m^2 subcutaneously at weekly intervals for the treatment of active WM. The Committee noted that the ESMO states that bortezomib may be administered alone or in combination with rituximab, noting that the addition of dexamethasone may also be beneficial (Kastritis et al. ESMO. 2018).

14.19. The Committee noted that the key evidence for the use of bortezomib for the treatment of WM comes from a prospective, multicentre, phase II study investigating the efficacy of BDR in 59 previously untreated symptomatic patients with WM. The Committee noted that study participants received a 21-day cycle of bortezomib alone (1.3 mg/m^2 IV on days 1, 4, 8, and 11), followed by weekly IV bortezomib (1.6 mg/m^2 on days 1, 8, 15, and 22) for 4 additional 35-day cycles, with IV dexamethasone (40 mg) and IV rituximab (375 mg/m^2) on cycles 2 and 5, for a total treatment duration of 23 weeks.

14.20. The Committee noted the long-term results of this trial after a median follow-up of 42 months. The Committee noted that the median PFS was 42 months with a 3-year survival of 81%. The Committee noted that the overall response rate (ORR) was 85% (95% confidence interval [CI] 73% to 92%). The Committee noted that the median IgM reduction after bortezomib monotherapy was 18% (range, 278% to 112%; 34% of patients had >25% reduction and 8% had >50% reduction). The Committee noted that 32 (54%) patients experienced disease progression or died, and that the main reasons for discontinuation of BDR were toxicity in 16 (27%) patients and disease progression (or death) in 5 patients (Dimopoulos et al. Blood. 2013;122:3276-3282).

14.21. The Committee noted the results of a 6-year minimum follow up analysis of the same trial (median duration of follow-up of 86 months). The Committee noted that the median PFS was 43 months (95% CI 23 to 63), and the 7-year PFS per International Prognostic Scoring System for WM (IPSSWM) was 62.5%, 42%, and 15% for low-, intermediate-, and high-risk disease, respectively. The Committee noted that the overall survival (OS) rate at 7 years was 66%, and the OS per IPSSWM was 87.5% for low-, 68.2% for intermediate-, and 48% for high-risk patients. The Committee noted that the ORR was 85%, and the median duration of response (DOR) was 64.5 months. The Committee noted that 40 patients (68%) progressed or died as a result of WM, whereas 9 patients (15%) died of unrelated causes, with peripheral neuropathy occurring in 46% patients (grade 2: 17%; grade >3: 7%) and neuropathic pain occurring in 20% (grade 3: n=1) (Gavriatopoulou et al. Blood. 2017;129:456-549)

14.22. In the absence of a relevant combination chemotherapy comparator arm in the key clinical trial above, the Committee noted the following evidence on the use of other agents currently funded for the treatment of WM:

- Zheng et al. Onco Targets Ther. 2019;12:2751-2766

- Walewski et al. Br J Haematol. 2020;188;898-906
- Laribi et al. Br J Haematol. 2018;186:146-149
- Kastritis et al. Blood. 2015;126:1392-4

14.23. The Committee considered that the evidence for the use of bortezomib for WM is of poor quality and that there are no head-to-head trials for this treatment in the requested indication. The Committee considered that, in the first line setting, those who would benefit most from bortezomib would be the 40% of those for whom BR is not suitable. The Committee considered that BDR is comparable to DRC, and that DRC would be preferred if neuropathy is present. The Committee considered that, in the second line setting (and in the absence of a BTK inhibitor), bortezomib would be an option for people with WM regardless of performance status and could follow first line DRC chemotherapy for those in which BR is not suitable (in the absence of neuropathy).

14.24. The Committee considered that, if access were to be widened, bortezomib would not replace BR in the first line setting, however that bortezomib would be comparable to DRC/R-CVP for those in which BR is not suitable. The Committee considered that in the second line setting, bortezomib (BDR) would be a good option, especially for those who have had DRC in the first line. The Committee however considered that if a BTK inhibitor were to be funded for first line or relapsed/refractory WM then this would be the preferred option.

Suitability

14.25. The Committee noted bortezomib is a subcutaneous injection used widely in New Zealand in both urban and rural outpatient settings.

Cost and Savings

14.26. The Committee considered that bortezomib was relatively inexpensive compared to other treatments for WM. The Committee noted that between 40 to 70 individuals per year could be eligible for treatment of treatment naïve or relapsed/refractory WM.

14.27. The Committee considered that, in a first line setting, bortezomib would most likely be considered for people with WM where BR chemotherapy is not suitable. The Committee considered that BR would not be suitable in approximately 40% of people requiring first-line treatment for WM, and these people could be treated with BDR. The Committee noted that currently either RCVP or CDR is the preferred treatment for those in which first-line BR is not suitable, with a roughly equal proportion of individuals between the two regimens.

14.28. The Committee considered that BR re-treatment would be suitable for less than 10% of people with relapsed/remitting WM, and that BDR would likely be considered for this group (regardless of performance status). The Committee noted that currently R, RCVP, or CDR is the preferred treatment for those in which second-line BR is not suitable, with a roughly equal proportion of patients between the three regimens.

Summary for Assessment

14.29. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator,

outcomes) information for bortezomib if it were to be funded in New Zealand for Waldenström macroglobulinemia. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with first-line WM where BR chemotherapy is not suitable	People with relapsed/refractory WM
Intervention	Bortezomib in combination with dexamethasone and rituximab (BDR) • Single 21-day cycle of bortezomib alone (1.3 mg/m^2 IV or SC on days 1, 4, 8, and 11) • Followed by weekly IV or SC bortezomib (1.6 mg/m^2 on days 1, 8, 15, and 22) for 4 additional 35-day cycles, with oral dexamethasone and IV rituximab (375 mg/m^2) 6 doses monthly, for a total treatment duration of 23 weeks	
Comparator(s) (NZ context)	*Roughly equal split of patient numbers among comparator treatment regimens* Dexamethasone, rituximab and cyclophosphamide (DRC) every 3 weeks for 6 cycles OR Rituximab combined with vincristine and prednisone (RCVP) every 3 weeks for 6 cycles	*Roughly equal split of patient numbers among comparator treatment regimens* Dexamethasone, rituximab and cyclophosphamide (DRC) every 3 weeks for 6 cycles OR Rituximab combined with vincristine and prednisone (RCVP) every 3 weeks for 6 cycles OR Rituximab monotherapy with 6 cycles of rituximab as currently funded or: *8-week course (two four-weekly cycles split 3 months apart) of rituximab 375mg/m^2.*
Outcome(s)	Increased progression free survival Increased overall response rate Potential overall survival benefit	

Table definitions:

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

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

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

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