PTAC Pharmacology and Therapeutics Advisory Committee

Objective advice to PHARMAC

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Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 22 and 23 August 2019

Records of PTAC and Subcommittees of PTAC are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016.

Note that this document is not necessarily a complete record of the meeting; only the relevant portions of the record relating to discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

PTAC and Subcommittees of PTAC may:

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

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

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

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

Contents

Record of attendance

PTAC members:
Mark Weatherall (Chair)
Marius Rademaker (Deputy Chair)
Alan Fraser
Brian Anderson
Giles Newton Howes
Jane Thomas
Jennifer Martin (via teleconference)
Matthew Strother
Melissa Copland
Sean Hanna
Simon Wynn Thomas
Stephen Munn
Tim Stokes

Apologies
None noted

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

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

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

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

1.4. PTAC and PTAC Subcommittees have complementary roles, expertise, experience, and perspectives:

- Both PTAC and PTAC Subcommittees are statutory advisory committees established by the PHARMAC Board (external to and separate from PHARMAC staff). Both provide objective advice to PHARMAC on community and hospital pharmaceuticals and their benefits, using the PHARMAC Factors for Consideration.

- PTAC considers Applications or PHARMAC staff proposals across all therapeutic groups in the Pharmaceutical Schedule. It has an overview view of Applications and other items referred to it for clinical advice. PTAC provides and promotes critical appraisal of strength and quality of evidence, applied rigorously, systematically and consistently across all therapeutic groups.

- PTAC Subcommittees provide objective advice within specific therapeutic areas. PTAC Subcommittees are separate from, and not subordinate to, PTAC. PTAC Subcommittees are appointed to reflect specialist knowledge and expertise in health needs and treatments within their own therapeutic groups/areas of clinical practice, including the applicability of evidence to clinical funding settings in New Zealand.

- PTAC and PTAC Subcommittees therefore provide separate and different, if complementary, perspectives and advice to PHARMAC. PTAC examines the same evidence with a different perspective from specialist expert PTAC Subcommittees, as do Subcommittees between them.

PTAC may therefore, at times, make recommendations that differ from PTAC Subcommittees', including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC Subcommittees may, at times, make recommendations that differ from PTAC's, or from other PTAC Subcommittees', when considering the same evidence.

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

2. Record of PTAC meeting held 23 and 24 May 2019

2.1. The Committee reviewed the record of the PTAC meeting held on **23 and 24 May 2019** and **agreed** that the meeting record be accepted.

3. Cardiovascular Subcommittee May 2019 meeting record

PTAC and PTAC Subcommittees may differ in the advice they provide to PHARMAC, including recommendations' priority, due to the committees' different, albeit complementary, roles, expertise, experience, and perspectives (see Section 1).

3.1. The Committee noted the record of the Cardiovascular Subcommittee meeting held on 8 May 2019.

3.2. Regarding item 1, the Committee noted item 1.8 that the Cardiovascular Subcommittee recommended PTAC should review its past recommendation regarding the application for the aspirin, atorvastatin and ramipril fixed dose combination product (Trinomia, a poly-pill) for secondary prevention of cardiovascular events in patients where adherence is suboptimal.

3.3. The Committee considered that its past advice was that PTAC should review this application if there was new evidence supporting its use in relation to outcomes that went beyond adherence; and that without this evidence it would be unable to recommend funding of fixed-dose combination products that were not cost-neutral to funding of each agent separately, taking into account drug acquisition and distribution costs to DHBs, and costs to the patient.

3.4. Regarding item 2.27, the Committee considered that clonidine should be reviewed by the Analgesic Subcommittee as part of its therapeutic group review.

3.5. Regarding item 3, the Committee considered that PHARMAC should consider its approach to funding companion diagnostic testing. The Committee considered that it could provide some advice to PHARMAC on applications for companion diagnostics as well as for medicines, once PHARMAC's approach to medical devices funding has been established.

3.6. Regarding item 4, the Committee noted the recommendation of the Subcommittee that alirocumab be funded in item 4.3 for people with heterozygous familial hypercholesterolaemia (HeFH) with a high priority. The Committee noted that there is a high health need and limited treatment options for this population group.

3.7. The Committee considered that alirocumab is a high cost medicine with uncertain cost-effectiveness. The Committee noted a recent publication regarding the cost-effectiveness of this agent which indicated a high cost per quality-adjusted life year (QALY) gained (Kazi et al. Ann Intern Med 2019;170:221-9).

3.8. The Committee noted that it had previously recommended another PCSK9 inhibitor, evolocumab, for decline at its November 2018 meeting. The Committee noted the Subcommittee had noted a mortality benefit in its review of the trial evidence for alirocumab (ODYSSEY study, with statistically significant all-cause mortality reduction: HR 0.86, 95% CI 0.79-0.93), in contrast to the trial evidence for evolocumab (FOURIER study, with no reduction: HR 1.05, 95% CI 0.91-1.19).

3.9. The Committee deferred endorsing the Subcommittee recommendations for alirocumab, based on the likely high cost of this medicine and uncertain cost-effectiveness, and recommended that PHARMAC staff conduct a preliminary cost-utility analysis regarding PCSK9 inhibitors and present this to PTAC for advice on clinical assumptions, where an eventual completed cost-utility analysis would help to inform PTAC's recommendation.

3.10. Regarding item 5, the Committee noted the Subcommittee's recommendation 5.3 that tafamidis be funded for the treatment of cardiac amyloidosis with a medium priority

based on a high health need, a lack of funded alternatives and a high cost of treatment.

3.11. The Committee noted a survival benefit associated with tafamidis.

3.12. The Committee noted there is no registered supplier of tafamidis in New Zealand and endorsed the Subcommittee's recommendation 5.4 that PHARMAC staff engage with Pfizer, the supplier of tafamidis internationally, and considered this engagement could clarify proposed registration pathways and the likely cost of this treatment.

3.13. The Committee recommended that it review the application for tafamidis, based on the likely high cost of this medicine, once there was a clear signal that a product would be registered in New Zealand.

3.14. Regarding item 6, the Committee considered that the mechanism of the health benefit for eplerenone in primary aldosteronism and resistant hypertension was likely similar to that of spironolactone.

3.15. The Committee noted the Subcommittee's recommendation 6.3 that access to eplerenone for patients with primary aldosteronism who are also intolerant of spironolactone be funded with a high priority. The Committee recommended that PHARMAC seek advice from the Endocrinology Subcommittee of PTAC regarding appropriate access criteria.

3.16. The Committee noted the Subcommittee's recommendation 6.4 that access to eplerenone for patients with resistant hypertension who are also intolerant of spironolactone be funded with a medium priority. The Committee recommended that PHARMAC conduct additional analyses to determine the size of this patient group and consequent budget impact.

3.17. Regarding item 7, the Committee noted that the Subcommittee did not reach consensus on the inclusion of right heart catheter studies in the Special Authority criteria for pulmonary arterial hypertension treatments. The Committee recommended that PHARMAC seek additional expert advice regarding the Special Authority criteria for pulmonary arterial hypertension treatments from the PHARMAC Pulmonary Arterial Hypertension Panel.

3.18. The Committee noted and agreed with the remainder of the record of the 8 May 2019 Cardiovascular Subcommittee meeting including the remaining recommendations 2.1, 2.23, 2.36, 8.3, 9.3, 9.4, and 9.5.

4. Anti-Infective Subcommittee May 2019 meeting record

4.1. The Committee noted and agreed with the record of the Anti-infective Subcommittee meeting held on 10 May 2019.

4.2. The Committee noted the Anti-infective Subcommittees view that cephalexin oral liquid should be made available on PSO. Members noted that flucloxacillin was unpalatable however they considered that this was not reason enough to widen access to cephalexin on a PSO. Members considered that cephalexin is more broad-spectrum than flucloxacillin and that prescriptions of cephalexin have been increasing, which has implications for antimicrobial stewardship and the development of anti-microbial resistance. Members considered that the highest health need would be for children requiring oral antibiotics for skin sepsis and that these scripts are free at present for under-14s. In rural areas, cephalexin is already available on PSO. Members considered that PHARMAC should investigate the cost of a palatable flucloxacillin oral liquid, which may cost significantly more.

4.3. The Committee noted PHARMAC are considering a competitive process for the integrase stand transfer inhibitor market (dolutegravir and raltegravir) in the treatment of HIV which may mean switching of therapies by current patients. Members considered that this is a sizable market that, if competed, access to both chemicals should be maintained for some specific patient groups such as pregnancy.

5. Cancer Treatment Subcommittee April 2019 meeting record

5.1. The Committee noted and agreed with the record of the Cancer Treatments Subcommittee of PTAC held on 5 April 2019, with the exception of item 4 regarding palbociclib in combination with fulvestrant for the second-line treatment of hormone-receptor (HR) positive, human epidermal growth factor receptor-2 (HER-2)-negative locally advanced or metastatic breast cancer.

5.2. The Committee noted that at the April 2019 meeting, in addition to review of the funding application for second-line use of palbociclib, CaTSoP had also reviewed information regarding other CDK4/6 inhibitors – ribociclib and abemaciclib.

5.3. The Committee noted that alongside CaTSoP's medium priority recommendation for second-line use of palbociclib specifically, CaTSoP had also made several recommendations regarding the class of agents in various settings, specifically that:

- CDK4/6 inhibitors for use as first-line treatment be funded with high priority;
- CDK4/6 inhibitors for use as second line treatment in patients with hormone-sensitive disease be funded with high priority; and
- CDK4/6 inhibitors for use in all second-line patients be funded with medium priority.

5.4. The Committee noted that the CaTSoP April 2019 record regarding palbociclib as a second-line treatment HR-positive HER-2-negative locally advanced or metastatic breast cancer had been considered by PTAC at its May 2019 meeting alongside its consideration of the funding for cyclin dependent kinase (CDK) 4/6 inhibitors (palbociclib, ribociclib and abemaciclib) for HR-positive HER2-negative locally advanced or metastatic breast cancer.

5.5. The Committee noted that at its May 2019 meeting, PTAC had recommended the applications for first-line use of palbociclib and ribociclib in combination with an aromatase inhibitor be funded with low priority, and the application for second line use of palbociclib in combination with fulvestrant be funded with medium priority.

5.6. The Committee noted that in May 2019, while it had made recommendations regarding the three funding applications submitted to PHARMAC, it had not assigned priority recommendations specifically to the class of agents in certain treatment settings considered by CaTSoP. However, PTAC had considered that the currently available evidence for palbociclib, ribociclib and abemaciclib suggests there is a class effect associated with CDK4/6 inhibitors for the treatment of HR-positive, HER2-negative locally advanced or metastatic breast cancer subject to the criteria recommended by CaTSoP.

5.7. The Committee recognised that there were some differences in the records of PTAC and CaTSoP's consideration of the funding applications for these agents, likely based on the different but complementary expertise, experience, and perspectives each committee brought to its consideration under the Factors for Consideration.

5.8. The Committee noted it would be useful that CaTSoP clarify its advice about CDK4/6 inhibitors so that PTAC could further consider its priorities and recommendations for this class of agents.

5.9. In particular the Committee asked if CaTSoP could provide a more detailed evidence review and discussion about:

- Why the health need of a second-line population was rated higher than the first-line setting, but that the recorded recommendation was that funding of CDK4/6 inhibitors as a class was a lower priority for use in second-line than in first-line.
- More details about CaTSoP's interpretation of the evidence for differences in outcomes such as for overall survival (OS), progression-free survival (PFS), and quality of life in both first- or second-line settings for late breast cancers.
- More details about CaTSoP's assessment the OS benefit, its magnitude, and precision, for the different treatment settings, and the evidence used for this advice.

5.10. The Committee noted the importance of evidence on the relationships between important surrogate outcomes, which can include PFS or Objective Response Rates, and OS and Health-Related Quality of Life, and health utilities; and that these are used as inputs into cost-utility analysis and PHARMAC's decisions. The Committee considered it was particularly important to document the health benefit associated with PFS related to disease states, and the evidence for these inputs, then translate these to generic health states and health utility benefits.

5.11. The Committee noted reports that OS is difficult to use as a primary endpoint in early HR-positive breast cancer, given now long survival times, even on standard therapy, and confounding from multiple lines of sequential therapy over many years; and that these features combine to necessitate much greater study power (and expense) if OS is the primary outcome in trials in this situation

5.12. The Committee also noted that many cancer treatment trials primary outcome measures are surrogate outcome measurements such as progression-free survival (PFS), disease-free survival (DFS) and relapse-free survival (RFS) and consequentially that randomised prospective cancer trial evidence is now seldom available for OS for use in health funding decisions.

5.13. The Committee considered it would be helpful to receive further comment from CaTSoP more generally about use of surrogate outcomes in cancer trials across cancer subtypes.

5.14. The Committee also considered that, in the context of CDK4/6 inhibitors, it would be particularly helpful to receive advice on: the strength and quality of available evidence for the use of surrogate outcomes specifically for locally advanced or metastatic breast cancers, particularly those that are HR-positive and/or HER2-negative, and thus the applicability of such outcomes data in this setting.

5.15. The Committee noted that further advice would be sought from CaTSoP regarding the funding of CDK4/6 inhibitors and the points outlined above at CaTSoP's next meeting in October 2019.

6. Trastuzumab – biosimilar for use in multiple indications

Application

6.1. The Committee reviewed an application for CT-P6, a biosimilar trastuzumab, for use in multiple indications (early breast cancer, metastatic breast cancer, and gastric cancer).

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

Recommendation

6.3. The Committee recommended that PHARMAC could progress a competitive procurement process for trastuzumab and considered that a managed change to a single trastuzumab biosimilar product, such as CT-P6, would be clinically acceptable for the treatment of HER2-positive early breast cancer and HER2-positive metastatic breast cancer.

6.4. The Committee requested the Cancer Treatment Subcommittee of PTAC (CaTSoP) provide PHARMAC any advice on implementation issues.

Discussion

6.5. The Committee noted that the application for CT-P6 (Herzuma) requested funding for the treatment of early breast cancer, metastatic breast cancer, and gastric cancer, subject to patent expiry.

6.6. The Committee noted that the intravenous preparation of the trastuzumab reference product (Herceptin) has been listed on the Pharmaceutical Schedule since 2005 and is currently funded in New Zealand for HER2-positive early and metastatic breast cancer.

6.7. The Committee noted that an application for intravenous trastuzumab for the treatment of HER2-positive advanced gastric cancer was recommended for decline by CaTSoP and PTAC in 2011 (PHARMAC application tracker: trastuzumab for gastric cancer). The Committee noted that PHARMAC made a decision to decline this application in July 2019. The Committee therefore considered that in the absence of new evidence relevant to gastric cancer, that the application for CT-P6 would be considered only for HER2-positive early and metastatic breast cancers.

6.8. The Committee considered that biosimilars are likely to play an important role in the field of oncology in the future, and that uptake will be dependent on clinician and patient confidence in regulatory processes and appropriate education.

6.9. The Committee noted that both the European Society for Medical Oncology and the American Society of Clinical Oncology have released position statements in support of biosimilar use in oncology (Tabernero et al. ESMO Open. 2017;16:e000142; Lyman et al. J Clin Oncol. 2018;36:1260-5).

6.10. The Committee noted that while the active biologic substance of a biosimilar is essentially the same as the innovator product, there can be minor differences in post-translational modification e.g. glycosylation, and quaternary structure due to molecular folding. However, the Committee considered there is also variation in the innovator product over time due to changes in manufacturing processes.

6.11. The Committee noted that CT-P6 has been approved by the EMA for use in the European Union, by the FDA for use in the United States, and by Medsafe for use in New Zealand for all the indications of the reference trastuzumab product. The Committee noted the comprehensive international regulatory processes regarding the safety and efficacy of biosimilars.

6.12. The Committee noted that the clinical development program for CT-P6 includes two un-published Phase 1 trials (Study CT-P6 1.5 and Study CT-P6 1.4) and one Phase 3 trial (Study CT-P6 3.2).

6.13. The Committee noted the two randomised, double-blind, controlled, single-dose Phase 1 studies conducted to investigate CT-P6: a pivotal pharmacokinetic study in health subjects (Study CT-P6 1.5), and a pilot study evaluating initial safety and

pharmacokinetics in healthy subjects (Study CT-P6 1.4). The Committee noted that the results of these studies are unpublished, but that there is a summary available in the European Medicines Agency Assessment report for CT-P6 (EMA Assessment Report. Herzuma. December 2017). The Committee considered that the results of these studies support the biosimilarity of CT-P6 with the reference trastuzumab product, from a pharmacokinetic perspective.

6.14. The Committee noted the randomised, double-blind, active-controlled, Phase 3 trial that aimed to establish the equivalence of CT-P6 and reference trastuzumab (Herceptin) in the treatment of 549 patients with HER2-positive early-stage breast cancer (Study CT-P6 3.2; Stebbing et al. Lancet Oncol. 2017;18:917-28). The Committee noted that the primary endpoint was pathological complete response (pCR) at the time of definitive surgery (following 24 weeks of neoadjuvant trastuzumab), and that pharmacokinetic, pharmacodynamic, and safety data were also collected. The Committee noted that regulators, including in Europe and the United States, have accepted pCR as a surrogate endpoint for efficacy, albeit the evidence appeared mixed on whether pCR is truly predictive of event-free survival and/or overall survival. The Committee also noted that it is unlikely that survival data will be forthcoming as it is not mandated for biosimilars approval.

6.14.1. The Committee noted that Stebbing et al. (2017) reported that 116 of 248 (46.8%) patients receiving CT-P6 achieved pCR compared with 129 of 256 (50.4%) patients receiving reference trastuzumab, and that the 95% confidence interval of the estimated treatment outcome difference was within the equivalence margin of -0.15 to 0.15 (outcome difference -0.04%; 95% CI -0.12 to 0.05). The Committee considered that the results from the secondary endpoints at the end of the neoadjuvant period were similar between the treatment groups.

6.14.2. The Committee considered that the safety profiles of CT-P6 and reference trastuzumab reported by Stebbing et al. (2017) were similar; treatment-emergent adverse events were reported in 19 of 271 (7%) patients receiving CT-P6 and 22 of 278 (8%) patients receiving reference trastuzumab, and serious adverse events included febrile neutropenia (4 [1%] CT-P6 vs 1 [<1%] reference trastuzumab) and neutropenia (1 [<1%] CT-P6 vs 2 [1%] reference trastuzumab).

6.14.3. The Committee noted that Stebbing et al (2017) reported that there were no notable differences in pharmacokinetic endpoints between the treatment groups at any cycle in the neoadjuvant period. The Committee noted that the EMA Assessment report provided further details on the pharmacokinetic findings from the Phase 3 trial, including a discussion of unexpected findings that were subsequently attributed to the assay platform used.

6.14.4. The Committee noted that antidrug antibodies can develop as a result of exposure to a drug, and that the biological role of these is unclear (antidrug antibodies can be neutralising, immunogenic, or present with no discernible effect). The Committee noted that 12 patients in the Phase 3 trial were antidrug antibody positive at baseline (all neutralising antibody negative), but that no patients were positive for antidrug antibodies in the adjuvant or post-treatment follow-up period (EMA Assessment Report. Herzuma. December 2017).

6.15. The Committee considered a randomised double-blind equivalence trial that investigated the safety and efficacy of switching patients with HER2-positive early breast cancer from reference trastuzumab to the biosimilar trastuzumab ABP 980, after neoadjuvant treatment with the reference product (von Minckwitz et al. Lancet Oncol. 2018;19:987-98). The Committee noted the conclusion of the study, which was that the lower bounds of the 90% confidence intervals for the risk ratio and risk difference showed non-inferiority but that the upper bounds exceeded the predefined equivalence margins, meaning the analysis of non-superiority was inconclusive. The

Committee noted that the reference trastuzumab product and ABP 980 had similar safety outcomes. The Committee noted there have been a number of switching studies between biosimilar formulations of rituximab.

6.16. The Committee considered that there is limited switching data available at this time specifically for CT-P6, and none relevant to breast cancer. The Committee also considered that there is no data available for the use of biosimilar trastuzumab in combination with other monoclonal antibody therapies e.g. pertuzumab, or for sequencing of therapies following biosimilar trastuzumab.

6.17. The Committee noted that that there are a number of biosimilar trastuzumab products undergoing regulatory approval internationally. The Committee noted that CT-P6 is the only biosimilar trastuzumab currently approved by Medsafe, but that there are two others currently under review.

6.18. The Committee considered that if CT-P6 or another biosimilar trastuzumab were to be funded, that there should be only one trastuzumab product listed on the Pharmaceutical Schedule to reduce the possibility of unmanaged switching, given the lack of biosimilar to biosimilar switching data available at this time. The Committee also considered that frequent switching between products is not desirable, and that the contract period for a listed product should be at least three years to minimise this (noting that this period exceeds the average duration of treatment for most patients, meaning the majority of patients would need to switch a maximum of once).

6.19. The Committee considered that if CT-P6 or any other trastuzumab biosimilar were to be funded, that a managed transition period of six months would be appropriate, provided immunogenicity is monitored.

6.20. The Committee considered that the nocebo effect (i.e. a negative outcome occurring due to a belief that the intervention will cause harm via adverse effects or a perceived lack of treatment benefit) will be a concern with biosimilars in oncology, particularly in the metastatic setting where disease progression is inevitable and may be attributed to a biosimilar switch without good evidence. The Committee considered that the nocebo effect depends highly on prescriber-patient interaction, and this could be particularly important in oncology.

6.21. The Committee considered that in future, it would continue to be appropriate for clinical advice to be sought on biosimilar products prior to a funding decision being made.

6.22. The Committee was generally supportive of biosimilars, and considered that these agents will play an increasingly important role in the oncology field. The Committee considered that the evidence available to date supports biosimilarity between CT-P6 and the reference trastuzumab product and that there is no evidence of any safety concerns.

6.23. The Committee considered that if CT-P6 or another biosimilar trastuzumab were to be funded, that it should be listed through a sole-supply process with a transition period of six months.

7. Pembrolizumab for the adjuvant treatment of resected stage III melanoma

Application

7.1. The Committee reviewed the application for pembrolizumab for the adjuvant treatment of resected stage III melanoma.

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

Recommendation

7.3. The Committee **recommended** that pembrolizumab for the adjuvant treatment of resected stage III melanoma be deferred, pending further data to support the benefit of use of pembrolizumab in this setting. The Committee considered that the data currently available for the benefits of treatment was insufficient to inform a funding decision.

7.4. The Committee requested advice from the Cancer Treatments Subcommittee of PTAC (CaTSoP) regarding the health need of this population, current surveillance requirements, and the interpretation of evidence for health benefit specifically regarding: the utility of recurrence-free survival (RFS) as a surrogate for OS in stage III melanoma; the impact of immune checkpoint inhibitors on the melanoma treatment landscape on RFS in patients with resected stage III melanoma; the likelihood and interpretation of overall survival (OS) data from Keynote-054 and other immune checkpoint inhibitor studies; consideration of class effect, optimal timing or sequencing of PD-1 inhibitor therapy in stage III and/or stage IV melanoma; patient number estimates; and appropriate proposed Special Authority criteria including response assessment requirements.

Discussion

7.5. The Committee noted that stage III melanoma is a malignant skin cancer which has spread locally, regionally or is in transit to a lymph node. The Committee noted that Ministry of Health data estimates that 6% of diagnosed melanoma cases in 2019 are stage III, equivalent to about 160 patients.

7.6. The Committee noted that the American Joint Committee on Cancer (AJCC) melanoma staging was updated in January 2018 from the 7th Edition to the 8th Edition, now classifying stage III melanoma into four subgroups (IIIA, IIIB, IIIC or IIID) rather than three, according to characteristics and the extent of lymph node involvement, and those of the primary tumour and nearby lesions. The Committee considered that this change in staging criteria will be seen in future clinical trial protocols and in standard of care guidelines, which may affect interpretation of clinical trial data due to the new classifications use of radiological, rather than pathological, methods for staging.

7.7. The Committee noted a US study of patients with stage III melanoma reported 5-year recurrence-free survival (RFS) of at least 63%, 32%, and 11% for stage IIIA, IIIB, and IIIIC melanoma, respectively (Romano et al. J Clin Oncol. 2010;28:3042-7). The Committee noted data from a single-centre, Australian study in which more than half of stage III melanoma cases had stage I or stage II melanoma which progressed to stage III, and noted that the 5-year RFS was 81.4%, 64.0%, 44.5% and 9.8% for stages IIIA, IIIB, IIIC and IIID, respectively, according to AJCC 8th Edition staging (Haydu et al. J Clin Oncol. 2017;35:1721-9). The Committee considered 5-year RFS was poor in patients with stage IIID disease, however, the data suggested a proportion of patients could potentially be cured by resection alone although this group is not currently clearly defined.

7.8. The Committee considered that standard care treatment for resectable stage III melanoma in New Zealand consists of curative surgical resection, sentinel lymph node removal and completion lymph node dissection for patients with stage IIIB disease or above. The Committee noted emerging evidence that performing complete lymph node dissection does not increase melanoma-specific survival in patients with melanoma and sentinel-node metastases (Faries et al. N Engl J Med. 2017;376:2211-

22; Leiter et al. Lancet Oncol. 2016;17:757-67), and this evidence has changed international guidelines; and considered this may affect the applicability of data from clinical trials that included mandatory complete lymph node dissection.

7.9. The Committee considered that most patients with resected stage III melanoma would be generally well (ECOG score 0), however, they would have a level of psychological distress that is not reported in the current literature, despite the existence of tools to measure this. The Committee noted that males are at higher risk of disease progression, as are patients with a higher stage of disease within the first 2 years after diagnosis.

7.10. The Committee noted that Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand (The Cancer Council Australia and Australian Cancer Network, Sydney and New Zealand Guidelines Group, Wellington [2008]) recommend observation for completely resected stage I-III melanoma without detail of specific surveillance. The Committee considered that current accepted care for patients whose stage III melanoma has been completely resected is observation only, by skin examination by a medical practitioner with or without ultrasound/radiological assessments. The Committee noted that the type and frequency of radiological assessments (including PET-CT) for surveillance varies between centres, and that use of MRI/CT/PET-CT is influenced by geographic location and access e.g. in the private setting.

7.11. The Committee noted that treatment for patients with unresectable or high-risk (stage IV) melanoma includes systemic e.g. chemotherapy, immunotherapy; or local therapies; e.g. radiotherapy, surgery, which are also given in different settings e.g. adjuvant, neoadjuvant, palliative.

7.12. The Committee noted that chemotherapy, immunotherapy or radiotherapy may be used internationally and in clinical trials for adjuvant treatment of melanoma, intended to reduce the risk of relapse and progression to metastatic disease. The Committee considered that adjuvant therapies are not widely used in New Zealand for resected stage III melanoma and that adjuvant interferon-alpha 2b (which is not funded in New Zealand) can lead to considerable toxicity with only a small benefit in overall survival.

7.13. The Committee noted the results of the randomised, double-blind, phase III CheckMate 238 trial of adjuvant nivolumab compared with ipilimumab in 906 patients with completely resected high-risk stage III melanoma, which reports 1-year RFS of 60.8% with ipilimumab and 70.5% with nivolumab (HR 0.65; 97.56% CI: 0.51 to 0.83; P<0.001) (Weber et al. N Engl J Med. 2017;377:1824-35 and also noted the updated results of the CheckMate 238 trial (Weber et al. J Clin Oncol. 2018;36(suppl; abstr 9502)). The Committee considered that nivolumab improved overall survival (OS) and had a better toxicity profile than ipilimumab.

Primary clinical trial evidence

7.14. The Committee noted that the pivotal trial evidence for the use of adjuvant pembrolizumab for the treatment of resected stage III melanoma is from the randomised (1:1), phase III, double-blind, placebo-controlled KeyNote-054 clinical trial which investigated pembrolizumab (200 mg) compared to placebo every 3 weeks for up to 1 year in 1,019 patients with completely resected high-risk stage III melanoma (Eggermont et al. N Enl J Med. 2018;378:1789-1801).

7.15. The Committee noted that the KeyNote-054 trial used AJCC 7th Edition tumour staging, included a large proportion of patients with stage IIIA disease, stratified patients by tumour stage and geographic location, and required patients to have had a complete lymph node dissection. Members considered that the trial had certainty of staging due to complete lymphadenectomies and pathological staging with AJCC 7th

Edition, compared to future trials which would be more reliant on radiological staging with AJCC 8th Edition. The Committee considered the trial inclusion and exclusion criteria were relevant to New Zealand patients except few New Zealand patients may now have complete lymph node dissections in standard care.

7.16. The Committee noted that the median RFS of the KeyNote-054 intention-to-treat population, the primary endpoint, was not reached and so not able to be estimated, with pembrolizumab compared to 20.4 months with placebo (95% CI: 16.2 to not estimable). The Committee noted one-year RFS was 75.4% with pembrolizumab compared to 61.0% with placebo: HR 0.57, 98.4% CI: 0.43 to 0.74, P<0.001.

7.17. The Committee considered there was little difference in RFS between patients with PD-L1 positive tumour status (HR: 0.54, 95% CI: 0.42 to 0.69, *P*<0.001) and PD-L1 negative tumour status (HR: 0.47, 95% CI: 0.26 to 0.85, *P*=0.01) who received pembrolizumab in the KeyNote-054 clinical trial. The Committee considered that the trial data suggests consistent RFS with pembrolizumab across various sub-groups.

7.18. The Committee considered that the KeyNote-054 trial demonstrated a significant effect on RFS but there is insufficient data to suggest this is associated with a clinically meaningful increase in OS. The Committee considered the quality of life benefits of adjuvant pembrolizumab were uncertain, given that patients with resected stage III melanoma are generally asymptomatic.

7.19. The Committee noted that the median duration of KeyNote-054 trial treatment was 12 months (15.1 months median follow up) and similar proportions of patients completed the treatment regimen in each group, however, 13.8% of pembrolizumab patients discontinued treatment due to toxicity and 35.7% of placebo patients discontinued treatment due to disease progression. The Committee noted that grade 3 to 5 adverse events occurred in a higher proportion of patients who received pembrolizumab (14.7%), including 1 treatment-related death, than placebo (3.4%).

7.20. The Committee considered that adjuvant pembrolizumab conveys significantly more adverse effects for patients with resected stage III melanoma, including the risk of a significant adverse reaction to immunotherapy. The Committee considered that grade 4 or 5 serious adverse events can be difficult to manage and require hospitalisation, multidisciplinary care and additional treatments e.g. steroids, infliximab.

7.21. The Committee noted a subsequent publication which assessed the prognostic and predictive values of AJCC 8th Edition staging on the KeyNote-054 trial patient cohort, reporting 1-year RFS in stage IIIA, IIB, IIIC and IIID of 92.7%, 79.0%, 73.6% and 50.0% respectively (Eggermont et al. Eur J Cancer. 2019: 116;148-57). The Committee considered that AJCC 8th Edition staging was strongly associated with RFS but did not have predictive importance for the treatment comparison in regard to RFS (*P* = 0.68).

7.22. The Committee considered that there is limited data for the use of adjuvant pembrolizumab, but since there may be a higher risk of relapse in the first 2-3 years, early treatment of patients diagnosed with stage IIIB melanoma or higher may be more suitable. However, the Committee considered that there is no evidence for whether the OS benefit would be greater with adjuvant pembrolizumab for stage III disease compared to treatment with pembrolizumab in the unresectable stage IV setting that is currently funded.

7.23. The Committee considered that the KeyNote-054 trial did not provide data for OS, sequencing of treatment, or evidence of benefit from further pembrolizumab treatment after relapse. The Committee considered that the relevance of the primary trial endpoint (RFS) and the external validity of the KeyNote-054 trial remained uncertain, although the individual trial was of high quality. The Committee noted that data

collection is ongoing to address the secondary endpoints of the KeyNote-054 trial including distant metastasis-free survival, OS, safety measures, and measures of health-related quality of life.

Recurrence-free survival as a surrogate outcome for overall survival

7.24. The Committee noted the results of a meta-analysis which included a total of about 5,000 patients with stage II or III melanoma from 11 studies comparing interferon to observation, and 1 study of interferon compared to vaccination (Suciu et al. J Natl Cancer Inst. 2018; 110. Doi: 10.1093/jnci/djx133). The Committee noted that the authors predicted that a hazard ratio of 0.77 or less for RFS would predict a benefit in OS.

7.25. The Committee noted that there is a statistical link between the probability of RFS and OS, although its external validity was unclear. The Committee considered that all studies used in the meta-analysis (published in 2010 to 2013) would have recruited participants before immunotherapy was widely used and therefore do not reflect current melanoma treatment paradigms, which presented challenges for validating this prediction.

7.26. The Committee considered that there is currently insufficient survival data to inform assessments of whether RFS is an appropriate surrogate outcome for OS in resected stage III melanoma, but given data collection from KeyNote-054 is ongoing, that OS data would likely be available ahead of sufficient data to assess RFS as a surrogate.

Pembrolizumab re-treatment

7.27. The Committee considered that both the relapse rate at 18 months from the start of adjuvant pembrolizumab, and the optimal duration of treatment for stage III melanoma, is yet to be identified. The Committee considered that there are no predictive biomarkers for ongoing treatment but that the evidence in this area e.g. tumour burden, is evolving.

7.28. The Committee noted that patients with stage III disease who have a clinical complete response to treatment before stopping (for reasons other than relapse/disease progression or adverse events), and then go on to have re-treatment upon progression, are more likely to respond to re-treatment than those patients whose best response was a partial response or stable disease (Jansen et al. Ann Oncol. 2019;30:1154-61).

7.29. The Committee considered that patients who relapse during adjuvant treatment with pembrolizumab were more likely to have a poor response to pembrolizumab re-treatment.

7.30. The Committee considered that there is limited (but ongoing collection of) data for the benefits and risks of pembrolizumab re-treatment for advanced or metastatic disease, in patients who previously had adjuvant pembrolizumab for resected stage III melanoma, and that there is insufficient data to identify, characterise and predict the size of a patient group who may respond to pembrolizumab re-treatment.

General

7.31. The Committee noted that the UK National Institute for Health and Care Excellence (NICE) had considered that the cost-effectiveness of adjuvant pembrolizumab was uncertain and that more evidence would be needed to address clinical uncertainties, however, adjuvant pembrolizumab met the criteria for inclusion in the Cancer Drugs Fund (NICE, 2018). The Committee noted a recent cost-effectiveness study in the US conducted using a Markov cohort model of KeyNote-054 patient-level data that

reported an incremental cost-effectiveness ratio said to be under the US threshold for funding (funding jurisdictions/settings not determined) (Bensimon. J Med Econ. 2019 23:1-13), but considered it this was not applicable to New Zealand due to base cost differences and New Zealand not having a threshold (Metcalfe et al. N Z Med J. 2012;125:99-101).

7.32. The Committee considered that adjuvant treatment of otherwise asymptomatic patients may not lessen any anxiety of the patient and family/whānau, and the regular hospital visits and infusions may result in a treatment burden that negatively impacts on family and whānau. Members noted that approximately 60% of patients with resected stage III melanoma would have prolonged RFS even without adjuvant treatment.

7.33. The Committee noted the supplier estimate of approximately 334 patients being suitable for this treatment in the first year (due to a backlog), with fewer patients in subsequent years. The Committee considered this estimate could be too high, however, noting the potential for increased referral from plastic surgery and dermatology services if pembrolizumab were to be funded in this setting. The Committee considered that CaTSoP or Oncology Societies in New Zealand may be able to better estimate patient numbers.

7.34. The Committee noted that adjuvant treatment of resected stage III melanoma would significantly impact on District Health Board (DHB) infusion services and also increase overall oncology service usage, as these patients are currently under observation rather than active treatment.

7.35. The Committee considered that the appropriate methods and frequency of surveillance for patients with resected stage III melanoma were unclear. The Committee considered that health resource costs would depend on what surveillance was required at what frequency and whether computed tomography (CT), ultrasonography (US) or positron emission topography (PET) scanning was used. Members considered that availability of PET scanning is limited, the cost of PET scans is high, and that there is limited data to support routine PET or even CT surveillance in stage III melanoma.

7.36. The Committee considered there would be a surge of high uptake initially, if adjuvant treatment with pembrolizumab were to be funded for resected stage III melanoma. The Committee considered that adjuvant pembrolizumab treatment may delay the use of other treatments for metastatic disease but is unlikely to reduce the usage of other agents.

7.37. The Committee considered that the data available for the benefits and risks of treatment was insufficient to inform a funding decision, and requested advice from the Cancer Treatments Subcommittee of PTAC (CaTSoP) to inform the assessment of health need in this patient group, the interpretation of health benefit in relation to the primary clinical trial evidence, and the potential sequencing of treatment with pembrolizumab (ie whether to start treatment at stage III or stage IV).

8. Tofacitinib for the treatment of rheumatoid arthritis

Application

8.1. The Committee reviewed an application for tofacitinib (Jaqinus) for the treatment of moderate to severe, active rheumatoid arthritis for patients who have had an inadequate response or are intolerant to methotrexate.

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

Recommendation

8.3. The Committee recommended that tofacitinib be funded with a **medium** priority for patients with rheumatoid arthritis under the same Special Authority criteria in place for adalimumab and etanercept.

8.4. The Committee recommended that tofacitinib be funded with a **medium** priority for patients with moderate to severe rheumatoid arthritis who were not adequately responding to tumour necrosis factor inhibitors, subject to the Special Authority criteria recommended by the Rheumatology Subcommittee:

Initial application – (rheumatoid arthritis) only from a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1. The patient has had an initial Special Authority approval for adalimumab and/or etanercept for rheumatoid arthritis; and
2. Either:
   2.1. The patient has experienced intolerable side effects from a reasonable trial of adalimumab and/or etanercept; or
   2.2. Following at least a four month trial of adalimumab and/or etanercept, the patient did not meet the renewal criteria for adalimumab and/or etanercept; and
3. Treatment is to be used as an adjunct to methotrexate therapy or monotherapy where use of methotrexate is limited by toxicity or intolerance.

Renewal – (rheumatoid arthritis) only from a rheumatologist or medical practitioner on the recommendation of a rheumatologist. Approvals valid for 6 months for applications meeting the following criteria:
Both:

1. Treatment is to be used as an adjunct to methotrexate therapy or monotherapy where use of methotrexate is limited by toxicity or intolerance; and
2. Either:
   2.1. Following 3 to 4 months of initial treatment, the patient has at least a 50% decrease in active joint count from baseline and a clinically significant response to treatment in the opinion of the physician; or
   2.2. The patient demonstrates at least a continuing 30% improvement in active joint count from baseline and a clinically significant response to treatment in the opinion of the physician.

Discussion

8.5. The Committee noted that the application for tofacitinib was considered by the Rheumatology Subcommittee in October 2017. The Committee noted that in October 2017, the Rheumatology Subcommittee recommended that tofacitinib should be funded for patients with moderate to severe rheumatoid arthritis who were not adequately responding to TNF inhibitors with a high priority, and that tofacitinib should be funded for patients with rheumatoid arthritis under the same Special Authority criteria in place for adalimumab and etanercept with a medium priority.

8.6. The Committee noted that rheumatoid arthritis is a debilitating chronic inflammatory disease characterised by progressive, irreversible joint damage, impaired joint function, and pain.

8.7. The Committee noted that initial treatment options for rheumatoid arthritis include conventional disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, sulfasalazine, hydroxychloroquine, ciclosporin, and leflunomide. The Committee noted that biologic DMARDs are initiated once a patient is not responding adequately to these agents.

8.8. The Committee noted that the first-line biologic DMARDs are adalimumab and etanercept, which are tumour necrosis factor (TNF) inhibitors delivered by subcutaneous injection and funded in the community and hospitals. The Committee noted that second- and third-line biologic DMARDs include infliximab, rituximab, and

tocilizumab, all of which are delivered via intravenous infusion and are only funded for use in hospitals.

8.9. The Committee noted, without necessarily accepting, the supplier's estimates that the prevalence of rheumatoid arthritis in New Zealand is approximately 3%, that approximately 20% of patients with rheumatoid arthritis are eligible for treatment with first-line biologic DMARDs, and that 30% of eligible patients are likely to receive treatment.

8.10. The Committee noted that the application being considered requested funding for tofacitinib for patients who have had an inadequate response or are intolerant to methotrexate, which would position tofacitinib in the same line of therapy as adalimumab and etanercept.

8.11. The Committee noted that tofacitinib is a selective inhibitor of the Janus kinase (JAK) family of enzymes, with primary activity against JAK1 and JAK3 and some activity against JAK2. The Committee noted that tofacitinib impairs the differentiation of CD4+ T helper cells, limits generation of pathogenic Th17 cells, blocks NK cell differentiation, and limits production of TNF and other proinflammatory cytokines.

8.12. The Committee noted that tofacitinib 5 mg twice daily is approved by Medsafe for the treatment of signs and symptoms of moderate to severe active rheumatoid arthritis in adults who have an inadequate response or are intolerant to methotrexate. The Committee noted that tofacitinib is indicated for use alone or in combination with non-biologic DMARDs, including methotrexate.

8.13. The Committee noted evidence provided by one Phase 2b and two Phase 3 trials that investigated the efficacy and safety of tofacitinib compared with placebo in patients with rheumatoid arthritis with an inadequate response to non-biologic DMARDs (Kremer et al. Arthritis Rheum. 2012;64:970-81; van der Heijde et al. Arthritis Rheum. 2013;65:559-70; Kremer et al. Ann Intern Med. 2013;159:253-61). The Committee noted that these studies all reported that tofacitinib in combination with standard of care improved disease control compared with placebo and had a manageable safety profile.

8.14. The Committee noted a 24-week, double-blind, Phase 2b trial that investigated the efficacy and safety of tofacitinib (1, 3, 5, 10, 15 mg twice daily) or adalimumab (40 mg subcutaneously every 2 weeks) monotherapy compared with placebo in 384 patients with rheumatoid arthritis with an inadequate response to non-biologic DMARDs (Trial 1035: Fleischmann et al. Arthritis Rheum. 2012;64:617-29). The Committee noted that patients receiving adalimumab were switched to tofacitinib 5 mg at 12 weeks. The Committee noted that the proportion of patients achieving an ACR20 response at week 12 was 31.5% in the 1 mg arm (P=0.256), 39.2% in the 3 mg tofacitinib arm (P≤0.05), 59.2% in the 5 mg arm (P<0.0001), 70.5% in the 10 mg arm (P<0.0001), 71.9% in the 15 mg arm (P<0.0001), and 35.9% in the adalimumab arm (P=0.105), compared with 22.0% in the placebo arm. The Committee noted that the proportion of patients achieving an ACR20, ACR50, and ACR70 response at Week 24 was significantly higher in the tofacitinib 5 mg, 10 mg, and 15 mg arms compared with placebo.

8.15. The Committee noted a 12-month, double-blind Phase 3 trial that investigated the efficacy and safety of tofacitinib (5 mg or 10 mg twice daily) or adalimumab (40 mg subcutaneously every 2 weeks) compared with placebo in 717 patients with rheumatoid arthritis with an inadequate response to methotrexate (Trial 1064; van Vollenhoven et al. N Engl J Med. 2012;367:508-19). The Committee noted that all patients in this trial were receiving background methotrexate. The Committee considered that the most pertinent results were the ACR20 response rates at Month 6 without advancement penalty: 60.7% of patients receiving tofacitinib 5 mg, 62.8%

of patients receiving tofacitinib 10 mg, and 58.3% of patients receiving adalimumab achieved an ACR20 response.

8.16. The Committee noted the Health Assessment Questionnaire disability index (HAQ DI) results from Trial 1035 (Fleishmann et al. 2012) and Trial 1064 (van Vollenhoven et al. 2012). The Committee considered that the improvements in HAQ-DI scores observed in patients who received tofacitinib were equivalent to those seen in patients who received adalimumab.

8.17. The Committee noted the results of a meta-analysis provided by the supplier that included Trial 1035 and Trial 1064. The Committee considered that the results of this pooled analysis demonstrated that the ACR50 response rates for tofacitinib were higher than adalimumab, and the ACR20 and ACR70 response rates were not significantly different between the agents.

8.18. The Committee noted the results of an indirect comparison provided by the supplier that compared tofacitinib (8 studies) with adalimumab (8 studies). The Committee considered that the results of this analysis indicated that tofacitinib was non-inferior to adalimumab as monotherapy and combination therapy. The Committee noted the exception in the analysis was for ACR50 response at 3 months, which did not demonstrate non-inferiority of tofacitinib compared with adalimumab.

8.19. The Committee noted the safety findings of the indirect comparison provided by the supplier. The Committee considered that patients receiving tofacitinib had a slightly higher risk of gastrointestinal adverse events and infections and infestations compared with patients receiving adalimumab, but that the incidence of other adverse events was similar.

8.20. The Committee considered that there is limited data available to compare tofacitinib with etanercept. The Committee considered that there are no head-to-head trials, and that indirect comparisons have limited value as the etanercept trials were conducted more than a decade before the tofacitinib trials.

8.21. Noting the above limitations, the Committee considered the indirect comparison of tofacitinib with etanercept provided by the supplier. The Committee considered that the results generally indicated that etanercept was superior to tofacitinib; however, members noted that the differences in patient population limited the value of this finding.

8.22. The Committee noted that there are concerns regarding the risk of herpes zoster infection (shingles) among patients receiving tofacitinib. The Committee noted that the incidence rates of herpes zoster infection in Trial 1035 and Trial 1064 were 2.8% among patients receiving tofacitinib and 1.9% among patients receiving adalimumab, and that these cases were all mild or moderate in severity. The Committee also noted the results of a review of 19 clinical studies which reported that the majority (~90%) of cases of herpes zoster infection among patients treated with tofacitinib were non-serious and involved only one dermatome (Winthrop et al. Arthritis Rheumatol. 2017;69:1960-1968). Members considered that pre-treatment vaccination against herpes zoster with a non-live vaccine will be important if tofacitinib is funded.

8.23. The Committee noted that there is an increased risk of cardiovascular disease among patients with rheumatoid arthritis. The Committee noted the results of a review of cardiovascular adverse events, blood pressure, and lipid level changes in patients receiving tofacitinib for rheumatoid arthritis, pooling data from six Phase 3 studies and two open-label long-term extension (LTE) studies (Charles-Schoeman et al. Semin Arthritis Rheum. 2016;46:261-71). The Committee noted that this study concluded that tofacitinib was associated with an increase in lipid levels within the first three

months of treatment, but that there was a low incidence of cardiovascular events (rate comparable to placebo).

8.24. The Committee noted a systematic review of serious adverse events occurring with ten biologic and targeted synthetic DMARDs for rheumatoid arthritis, including tofacitinib (Tarp et al. Rheumatology [Oxford]. 2017;56:417-25). The Committee considered that this study broadly indicated that the incidence of serious adverse events was similar between agents except for certolizumab, which appeared to be associated with a higher incidence of serious adverse events compared with other agents.

8.25. The Committee noted that the long-term safety of tofacitinib has been investigated in two extension studies: Trial 1041 and Trial 1029. The Committee noted a summary of the results provided by the supplier that indicated that the safety profile of tofacitinib long-term was consistent with the results observed in the Phase 2 and 3 trials.

8.26. The Committee noted that the U.S. Food and Drug Administration has approved a warning of an increased risk of blood clots and death with tofacitinib 10 mg twice daily dosing. The Committee considered that this is likely to be of more concern for indications other than rheumatoid arthritis that require higher daily doses e.g. ulcerative colitis).

8.27. The Committee considered that if tofacitinib were to be funded, it is likely that clinicians would continue to prescribe adalimumab or etanercept as first-line biologic DMARDs for rheumatoid arthritis, due to their familiarity with these agents and the increased risk of herpes zoster infection associated with tofacitinib. The Committee considered that exceptions would be where an oral medication would be preferred over a subcutaneous injection.

8.28. The Committee considered that the evidence available adequately demonstrates that tofacitinib with or without methotrexate to be non-inferior to adalimumab for the treatment of rheumatoid arthritis, and that the safety profile of tofacitinib is manageable.

8.29. The Committee accepted the Rheumatology Subcommittee's consideration that the health need for an alternative treatment was greatest for patients who were not adequately responding to TNF inhibitors, but noted that there is limited evidence for this patient group. The Committee therefore considered it would be reasonable to recommend the use of tofacitinib in this population, but only with a medium priority.

9. Mirabegron for the treatment of overactive bladder

Application

9.1. The Committee reviewed the clinician application for mirabegron for the treatment of overactive bladder.

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

Recommendation

9.3. The Committee **recommended** that mirabegron should be funded only if cost-neutral to oxybutynin due to a similar health benefit compared to currently funded agents,

Discussion

9.4. The Committee noted that overactive bladder syndrome is a urological condition defined as urinary urgency, with or without incontinence, and is frequently associated with nocturia (needing to urinate at night). Overactive bladder can result from a range of causes, and while not all cases can be cured, therapy can lead to symptom improvement for many patients.

9.5. The Committee noted that the prevalence of overactive bladder is approximately 16% based on data from the USA and Europe, older people are disproportionately affected (New Zealand data is sparse, however, the Australian Therapeutic Goods Administration [TGA] states that up to 30% of people over 75 years of age have overactive bladder), and it occurs more commonly in females than men (with a ratio of 6:1). Members considered that patients over 75 years of age would be the target population sought for this funding application.

9.6. The Committee considered that the severity of overactive bladder would vary among individuals, which would impact on the health need of patients. Members considered that individuals with overactive bladder are a broad group, and that this is an example of a normal physical process being medicalised and targeted, e.g. by direct advertising to consumers (DTCA) as requiring medical treatment, resulting in over-diagnosis (including self-diagnosis), both of which contribute to a risk of unnecessary overtreatment in this patient population.

9.7. Members considered that overactive bladder can affect family and whānau and noted evidence that suggests that overactive bladder patients who have cognitive impairment may have an increased likelihood of the need to move into a care facility (Luppa et al. Dement Geriatr Cogn Disord. 2008:26;65-78), although Members considered that overactive bladder, on its own, is not generally a significant contributing factor triggering the decision for patient admission to a care facility.

9.8. The Committee considered that international treatment strategies for overactive bladder use sequential approaches, progressing to the next step if desired outcomes are not achieved and start with patient/carer education, then behavioural treatment, addition of anticholinergic agents (specifically antimuscarinic medications), reassessment and further diagnostic assessments, and then more invasive treatments in selected patients.

9.9. The Committee noted that current medications used to treat overactive bladder in New Zealand are anticholinergic agents including oxybutynin (funded without restriction), solifenacin (funded, but with hospital use restricted to use in patients with overactive bladder and a documented intolerance of, or non-response to, oxybutynin), and tolterodine (funded, but restricted to use in patients with overactive bladder and a documented intolerance of, or non-response to, oxybutynin). The Committee noted that about 32,000 New Zealand patients receive treatment with one of these agents.

9.10. The Committee considered that alternative treatment options for patients in New Zealand with overactive bladder include pelvic floor exercises, sacral nerve stimulator implant and other surgical interventions (where surgery, for urinary stress incontinence, can inadvertently worsen overactive bladder in patients who present with mixed stress/urge incontinence) and intravesical Botulinum toxin injections (which are more difficult to use in elderly patients and require confirmation of diagnosis by urodynamic studies in symptomatic patients).

9.11. The Committee noted that the applicant states that there are New Zealand patients with overactive bladder who cannot tolerate anticholinergics, and patients who have concurrent incontinence and cognitive impairment or dementia. The Committee noted that the oxybutynin data sheet states that it should be used with caution in elderly patients who are at higher risk of developing cognitive impairment due to oxybutynin (Source: Apo-oxybutynin data sheet, March 2018), and considered that clinical

experience provides similar caution. The Committee was concerned that NHI-linked dispensing data indicate about 440 New Zealand patients receive both a cholinesterase inhibitor for dementia (rivastigmine or donepezil) and an anticholinergic for overactive bladder (oxybutynin, solifenacin or tolterodine).

9.12. The Committee considered that the evidence for cognitive impairment due to anticholinergic treatment of overactive bladder to be sparse, confined to a follow-up of 69 patients diagnosed with Alzheimer's dementia receiving donepezil (of which 16 patients were on anticholinergic agents) which reported after 2 years that Mini-Mental State Examination (MMSE) scores were worse for patients receiving anticholinergics (Lu et al. Am J Geriatr Psychiatry. 2003;11:458-61). The Committee noted that patients who have dementia were more likely to be prescribed an anticholinergic (Roe et al. J Am Geriatr Soc. 2002:50;836-42) and that there was an association, which is not necessarily causal, between the odds of dementia and anticholinergics (50% increase in odds of dementia within 10 years), although interpretation in the context of prevalent mild dementia in older age is required (Coupland et al. JAMA Intern Med. 2019; 179:1084-93).

9.13. The Committee noted that mirabegron is a beta-3 agonist that relaxes the bladder detrusor muscle, facilitating improved urine storage in the bladder without affecting the voiding process. The Committee noted that mirabegron is manufactured as 25 mg and 50 mg tablets and the applicant proposed dosing of 50 mg once daily. The Committee noted that mirabegron is not approved by Medsafe and there is no New Zealand supplier for this product.

9.14. The Committee noted that the clinical trial evidence for mirabegron predominantly consists of trials comparing mirabegron with tolterodine, some comparing with solifenacin, and none directly comparing mirabegron with oxybutynin. The Committee noted that published clinical trials included patients over 18 years of age with symptoms of overactive bladder for more than 3 months, with urinary frequency (more than 8 micturitions in 24 hours) and urgency (more than 3 urge episodes in 24 hours), with or without urinary incontinence.

Evidence

9.15. The Committee noted the results of the randomised (1:1), phase IIIb, double-blind, non-inferiority BEYOND trial of mirabegron (50 mg once daily) compared to solifenacin (5 mg once daily) for 12 weeks in 1,887 patients whose previous treatment with antimuscarinic agents was ineffective (Batista et al. Ther Adv Urol. 2015:7;167-79). The Committee noted that the adjusted mean number of micturations per 24-hours was 2.95 (SE 0.09) with mirabegron compared to 3.13 (0.09) with solifenacin, and considered that mirabegron had similar efficacy to solifenacin. The Committee noted that treatment-related adverse events (AEs) occurred in a greater proportion of solifenacin patients (14.5%) than mirabegron patients (11.1%) in the BEYOND trial, including dry mouth (5.8% solifenacin compared with 3.1% mirabegron), and that patient reported outcomes (PRO) showed superiority of solifenacin in four out of five assessments.

9.16. The Committee noted the results depicted for the randomised, phase II, double-blind, parallel, placebo and monotherapy-controlled Symphony trial of several dose schedules of solifenacin and mirabegron as monotherapy and in combinations for 12 weeks in 1,306 patients (Abrams et al. Eur Urol. 2015:67;577-88). The Committee noted that the adjusted change in mean number of micturations per 24-hours was greater with 10 mg solifenacin monotherapy than with either 25 mg and 50 mg doses of mirabegron monotherapy, and that the adjusted change in mean volume voided was similar with 10 mg solifenacin compared to 50 mg mirabegron. The Committee noted that the adjusted change in mean number of urgency episodes was reduced with 10 mg solifenacin and was slightly increased with 50 mg mirabegron. The

Committee considered that, based on this data, mirabegron offers roughly the same or slightly less health benefit as solifenacin.

9.17. The Committee noted that the Symphony trial did not provide safety data regarding cognitive changes. The Committee noted that there was a higher rate of serious AEs with mirabegron 50 mg (2.6%) than with solifenacin 10 mg (1.3%), the same proportion of patients discontinued treatment due to treatment-emergent AEs in each of these two treatment groups (2.6%), and the most frequent AEs with each treatment were hypertension (14.1% of patients with mirabegron 50 mg) and dry mouth, which is expected with anticholinergic agents (29.5% of patients with solifenacin 10 mg).

9.18. The Committee noted the results of a meta-analysis comparing mirabegron (25 mg, 50 mg and 100 mg) with tolterodine (4 mg) and with placebo in a total of 5,117 patients over 65 years of age, pooled from three 12-week trials and one 1-year trial (Wagg et al. Age Ageing. 2014:43;666-75). The Committee noted that mirabegron 50 mg was associated with a greater adjusted change in the number of incontinence episodes per 24-hours and the number of micturitions per 24 hours (-0.40 and -0.55, respectively) compared with tolterodine (-0.10 and -0.25, respectively) in all patients. The Committee noted that patients over 75 years of age had higher rates of treatment-emergent AEs, hypertension and discontinuation at 12 weeks with tolterodine and had higher rates of treatment-emergent AEs, discontinuations and serious AEs at 1 year with mirabegron 50 mg.

9.19. The Committee noted the results of a phase III, double-blind, randomised (1:1:1), active-controlled trial comparing 12 months' treatment with mirabegron (50 mg or 100 mg) or tolterodine 4 mg in 2,444 adult patients (Chapple et al. Eur Urol. 2013: 63;296-305). The Committee considered that the results showed mirabegron had greater efficacy than tolterodine and the safety data included roughly the same incidence of hypertension and cardiac AEs (including major adverse cardiovascular events; MACE) between treatment groups, although no cognitive AE data was reported. The Committee noted that there was no difference in patient-reported outcomes (PRO) between treatment groups.

9.20. The Committee noted the results of a phase III, double-blind, parallel-group, trial comparing mirabegron (50 mg or 100 mg), tolterodine (4 mg) and placebo for 12 weeks in 1,978 adult patients (Khullar et al. Eur Urol. 2013:63;283-95). The Committee considered that the results indicated mirabegron has superior efficacy compared with tolterodine for incontinence and frequency (although there was a small clinically significant difference compared with placebo) and that the safety data was similar to other studies although no cognitive AE data was reported. The Committee considered that the PRO data suggested that mirabegron was equivalent to tolterodine, based on 3 PRO assessment measures.

9.21. The Committee noted the results of the PREFER trial; a phase IV, double-blind, 8-week crossover, randomised (5:5:1:1) trial of mirabegron-tolterodine, tolterodine-mirabegron, mirabegron-mirabegron, or tolterodine-tolterodine (separated by a 2 week washout period) in 358 treatment-naïve adult patients (Staskin et al. Int Urogynaecol J. 2018:29;273-83). The Committee noted that the dose of mirabegron was increased halfway through this crossover study and considered that the results provide information on treatment sequencing with the second agent being preferred. The Committee considered that mirabegron was tolerated better than tolterodine and noted that PRO were similar between treatment groups in the PREFER trial (Herschorn et al. Health Qual Life Outcomes. 2018:16;69).

9.22. The Committee noted the results of a retrospective, longitudinal, observational study of 21,996 adult patients in the UK, which investigated persistence and adherence with mirabegron compared to other agents including oxybutynin, solifenacin and tolterodine (Chapple et al. Eur Urol. 2017:72;389-99). The Committee noted that a

small proportion of patients were on mirabegron (5.5%) but they were more likely to stay on treatment (38% persistence at 12 months) and tolerate it better (median time to discontinuation of 169 days) than patients on tolterodine (20% and 56 days, respectively) or patients on other agents.

9.23. The Committee noted the results of a systematic review of 44 randomised controlled trials including 27,309 patients, which assessed the comparative efficacy and safety of mirabegron, oxybutynin, solifenacin, tolterodine and other agents (Maman et al. Eur Urol. 2014:65;755-65). The Committee considered that the body of evidence indicates that solifenacin provides the same or slightly greater health benefit than mirabegron, and that mirabegron provides greater health benefit than tolterodine. The Committee considered that the evidence did not identify a patient group that would benefit most from mirabegron.

9.24. The Committee considered that the clinical significance of the small reported changes in urination was unclear but would likely have only minimal effects on patient's lives, and that the clinical trials were well-conducted but of short duration and lacked cognitive AE data, noting that a systematic review reported central nervous system (CNS) AEs were reported in less than a quarter of trials investigating antimuscarinic agents for overactive bladder (Paquette et al. J Am Geriatr Soc. 2011:59:1332-9). The Committee considered the efficacy and safety of mirabegron was not affected by concomitant beta blocker use, although mirabegron may be contraindicated in older patients on beta blockers for severe hypertension. The Committee considered that the safety profile data for mirabegron was similar to placebo and tolterodine in regard to MACE, cardiac AEs and hypertension.

General

9.25. The Committee considered that funding of mirabegron would not change the number of GP or specialist visits required, or change any other health system resource usage, compared to the currently funded agents. The Committee noted systematic review evidence suggesting that overactive bladder can increase the likelihood of a patient being moved into a care facility (Luppa et al. Dement Geriatr Cogn Disord. 2008:26;65-78) but that some members questioned the quality of this evidence.

9.26. The Committee considered that a very large number of patients may wish to access mirabegron, especially if the treatment is advertised to consumers e.g. on television, and that mirabegron would likely replace anticholinergic agents for patients who were unsuitable for, or couldn't tolerate, those agents. The Committee considered that there is a high risk of high mirabegron uptake from patients currently on anticholinergic agents, including the 440 patients with dementia and patients for whom other anticholinergics have poor efficacy.

9.27. The Committee considered that the following Special Authority criteria for mirabegron would be reasonable in the event that the product ever became less expensive, but could be revised to further restrict access to patients on cholinesterase inhibitors and to specify use as monotherapy:

MIRABEGRON - Special Authority for Subsidy
Initial application from any relevant practitioner. Approvals valid without further renewal unless notified, where patient has overactive bladder and meets the following criteria:
All of the following:

1. Patient has overactive bladder; and
2. Either:
    a. Anticholinergics are contraindicated due to concurrent dementia or cognitive impairment; or
    b. All funded anticholinergics have been trialled and the patient is intolerant of these agents.

9.28. The Committee considered that, should patients with overactive bladder be unable to receive oxybutynin, solifenacin and tolterodine would address this need (both agents

being non-inferior to oxybutynin and being relatively safe). The Committee considered that mirabegron provides a similar health benefit to available agents but is associated with a fiscal risk of high uptake.

10. Tolvaptan for the treatment of autosomal dominant polycystic chronic kidney disease (ADPKD)

Application

10.1. The Committee reviewed the application for tolvaptan for the treatment of autosomal dominant polycystic chronic kidney disease (ADPKD) from Otsuka Australia Pharmaceutical Pty Ltd.

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

Recommendation

10.3. The Committee **recommended** that tolvaptan for the treatment of autosomal dominant polycystic chronic kidney disease (ADPKD) be listed with a high priority due to the high health need of this patient group and the evidence for a benefit from tolvaptan, subject to the following Special Authority criteria:

TOLVAPTAN - Special Authority for Subsidy
Initial application - (autosomal dominant polycystic kidney disease) from a renal physician or on the recommendation of a renal physician. Approvals valid for 3 months for applications meeting the following criteria:
All of the following:

1. Patient has a confirmed diagnosis of autosomal dominant polycystic kidney disease (ADPKD); and
2. Patient has an eGFR of between 25 and 65 mL/min/1.73 m^2 at treatment initiation; and
3. Patient's disease is rapidly progressing, defined as either:
    a. A decline in eGFR of greater than or equal to 5 mL/min/1.73 m^2 within one-year; or
    b. An average decline in eGFR of greater than or equal to 2.5 mL/min/1.73 m^2 per year over a five-year period.

Note: Tolvaptan must be initiated and monitored under the supervision of physicians with expertise in managing ADPKD, and a full understanding of the risks of tolvaptan therapy including hepatic toxicity and monitoring requirements (liver function tests are required prior to tolvaptan initiation, monthly for the first 18 months and 3-monthly thereafter; concurrent monitoring for symptoms of possible liver injury is recommended).

Renewal - (autosomal dominant polycystic kidney disease) from a renal physician or on the recommendation of a renal physician. Approvals valid for 3 months for applications meeting the following criteria:
All of the following:

1. Patient has previously received tolvaptan for confirmed ADPKD; and
2. The treatment remains appropriate and the patient is benefitting from treatment; and
3. Patient has not developed end-stage renal disease (defined as an eGFR of less than 15 mL/min/1.73 m^2); and
4. Patient has not undergone a kidney transplant.

Note: Tolvaptan must be monitored under the supervision of physicians with expertise in managing ADPKD, and a full understanding of the risks of tolvaptan therapy including hepatic toxicity and monitoring requirements (liver function tests are required monthly for the first 18 months and 3-monthly thereafter; concurrent monitoring for symptoms of possible liver injury is recommended).

10.4. The Committee considered that it would like to be informed of the outcome of PHARMAC's economic modelling and considered that PHARMAC may need to prioritise different subgroups.

Background

10.5. The Committee noted that in December 2016 the Nephrology Subcommittee reviewed a clinician application for tolvaptan for autosomal dominant polycystic chronic kidney disease (ADPKD), and that the Subcommittee had recommended that tolvaptan for patients with autosomal dominant polycystic kidney disease (ADPKD) be listed on the Pharmaceutical Schedule with a high priority if a registered product becomes available. The Committee noted that a new funding application for tolvaptan was received from Otsuka Australia Pharmaceutical Pty Ltd. in May 2018 and that tolvaptan was Medsafe-registered in May 2019.

Discussion

10.6. The Committee noted that ADPKD is a complex, progressive, systemic genetic condition characterised by an increase in the number and size of fluid-filled cysts in the kidney. Members noted that ADPKD usually appears in teens, progressively increases kidney size, decreases renal function (glomerular filtration rate; GFR) far more rapidly than the natural decline with increasing age, and leads to end stage renal disease (ESRD) before the age of 60 years. Members considered that ADPKD patients with chronic kidney disease (CKD) stage II and III will have progressive disease resulting in early death (in their 40s and 50s), with a pattern seen in other affected family members, although some patients may progress slowly such that ESRD may not prior to death from other causes. The Committee considered that patients with severe, progressing disease have an especially high health need.

10.7. The Committee noted that there are no disease-modifying treatments available for ADPKD and that standard of care in New Zealand is supportive care only. The Committee noted that patients with CKD will eventually require dialysis costing ~$70,000 per patient per year and may require kidney transplant costing ~$100,000 initially and then ~$13,000 per patient per year. Members noted that most kidney transplants in New Zealand are performed in Auckland, of which about 20% are pre-emptive for patients with GFR of 15 mL per min per 1.73m^2. Members considered that kidney transplant would provide a significant benefit for patients on dialysis but would reduce life expectancy in patients who did not really need transplant (because of peri-operative mortality).

10.8. The Committee noted the supplier estimate of approximately 2,000 patients in New Zealand with ADPKD, and noted that ADPKD contributes to about 5% of ESRD (ANZDATA Registry, 41st Report, 2018). The Committee noted that in December 2016, the Nephrology Subcommittee considered that the incident population of patients with ADPKD in New Zealand is approximately 25 per year, and that Europeans aged between 18 and 50 years were predominantly affected, although the disease also affects Māori (rarely) and children (occasionally).

10.9. The Committee noted that Māori patients with chronic kidney disease are marginalised by factors including delayed diagnosis, fear of dialysis, and lack of cultural and individual considerations during medical care and treatment decision-making (Walker et al. BMJ Open. 2017;7:e013829). The Committee considered that family and whānau of patients with CKD are impacted by the requirements and logistics of treatment, and the disease affects the social lives of affected individuals.

10.10. The Committee noted that tolvaptan is a vasopressin V2 antagonist that inhibits vasopressin, resulting in increased urine output and reduced urine osmolality. The Committee noted that tolvaptan was approved by Medsafe in May 2019 and is indicated for slowing the progression of cyst development and renal insufficiency of ADPKD in adults with initial CKD stage 1 to 4 with evidence of rapidly progressing disease.

10.11. The Committee noted that the evidence for tolvaptan comes from two phase III, placebo-controlled, double-blind clinical trials: TEMPO 3:4 and REPRISE.

10.12. The Committee noted the primary publication from the randomised (2:1) TEMPO 3:4 trial, which investigated split-dose tolvaptan compared to placebo in 1,445 patients aged 18-50 years with ADPKD, total kidney volume (TKV) of at least 750 mL and estimated GFR (eGFR) of at least 60 mL per min per 1.73m^2 (Torres et al. N Engl J Med. 2012;367:2407-18), and the results of a post-hoc analysis by CKD stage at baseline (Torres et al. Clin J Am Soc Nephrol. 2016:11;803-11), both of which were reviewed by the Nephrology Subcommittee in December 2016.

10.13. The Committee noted that the primary objective of the TEMPO 3:4 trial was to assess the change in TKV over 3 years and that the authors reported a 49.2% reduction in kidney growth rate with tolvaptan compared with placebo in the intention-to-treat population (P<0.001), although the Committee considered that there was substantial variation in the values for TKV change in both patient groups (Torres et al. 2012).

10.14. The Committee noted the TEMPO 3:4 trial authors reported a statistically significant 26% difference in the annual change in eGFR (0.977 mL per min per per 1.73m^2) between tolvaptan and placebo (95% CI 0.60 mL per min per 1.73m^2 to 1.36, P<0.001) (Torres et al. 2012).

10.15. The Committee noted there was preservation of kidney function (P<0.001) and a lower risk of kidney pain requiring intervention (P=0.007) with tolvaptan compared to placebo (Torres et al. 2012). The Committee considered these outcomes were important for patients with ADPKD especially those with kidney pain, which can be extreme in ESRD.

10.16. The Committee noted that the TEMPO 3:4 trial included patients with CKD stages 1 to 3 and considered that the proportion of patients with stage 3b CKD (eGFR 30 to 44; N = 42, 3%) was small (Torres et al. 2012). The Committee considered that the trial eligibility criteria specifically selected a patient population with rapidly progressing disease. The Committee considered that the 3-year treatment duration was a limitation of the study. The Committee also noted the following published evidence from the TEMPO 3:4 trial:

10.16.1. Torres et al. Nephrol Dial Transplant. 2018:33;477-489 - TEMPO 4:4 open-label extension trial (additional 2 year follow up of TEMPO 3:4)

10.16.2. Cornec-Le Gall et al. Nephrol Dial Transplant. 2018:33;645-52 - TEMPO 3:4 post-hoc analysis of PROPKD score

10.17. The Committee noted that severe (grade 3 and higher) hepatic dysfunction occurred in 2-4% of TEMPO 4:4 trial patients (Torres et al. 2018). The Committee noted that major known adverse effects of tolvaptan are idiosyncratic hepatic toxicity with hepatic dysfunction occurring 3 to 18 months after treatment starts, and aquaresis-related adverse events (Source: Medsafe Data Sheet, May 2019).

10.18. The Committee noted the results of the randomised (1:1) REPRISE trial, which investigated split-dose tolvaptan compared to placebo in 1,370 patients with ADPKD aged 18-55 years with eGFR between 25 and 65 mL per min per 1.73m^2 and aged 56 to 65 years with eGFR between 25 and 44 mL per min per 1.73m^2 (Torres et al. N Engl J Med. 2017:377;1930-42).

10.19. The Committee noted that REPRISE provided further data on tolvaptan treatment and included patients over 50 years of age (which was considered important by the Nephrology Subcommittee, although it included only a small proportion (~8%) of non-Caucasian patients). The Committee noted that the trial eligibility criteria targeted

patients with severe disease, and considered that the trial patient group would equate to approximately a quarter of the patient population with ADPKD due to variation in disease progression and therefore ~75% of patients with less severe disease were excluded from the trial.

10.20. The Committee noted that the primary objective of the REPRISE trial was to assess the change in renal function (eGFR) from baseline to follow-up, and that the authors had reported a statistically significant 30% difference in the change in eGFR (1.27 mL per min per per 1.73m^2) between tolvaptan and placebo at 1 year (95% CI 0.86 mL per min per 1.73m^2 to 1.68, *P*<0.001) (Torres et al. 2017).

10.21. The Committee noted that most participants adhered to the trial treatment, and discontinuation due to adverse events (AEs) occurred in 9.5% of patients who received tolvaptan compared with 2.2% of patients who received placebo (Torres et al. 2017). The Committee noted that serious hepatic AEs were reported in 4.6% of patients who received tolvaptan compared to 0.6% of patients who received placebo in the REPRISE trial. The Committee noted that these events were not fatal and the liver effects were reversed after stopping treatment.

10.22. The Committee noted the supplier had stated tolvaptan provides one extra year of kidney life for every four years of treatment, and considered that this would be through delayed time to start of dialysis.

10.23. The Committee noted that the TEMPO 3:4, TEMPO 4:4 and REPRISE trials provide no evidence for tolvaptan use in children with ADPKD, and that there is limited inclusion of non-Caucasian patients with ADPKD. Members considered there is limited long-term data for delayed dialysis and kidney transplant. The Committee considered that tolvaptan provides a benefit for patients with ADPKD and CKD stage 2 or 3 disease, although this effect is difficult to quantify.

10.24. The Committee noted the results of an exploratory analysis modelling the long-term benefits of tolvaptan on renal function decline in ADPKD to predict natural disease progression with renal function decline based on that of the TEMPO 3:4 trial, which was compared with the TEMPO 4:4 and REPRISE trials (Bennett et al. BMC Nephrol. 2019;20:136). The Committee noted that the analysis of simulated patients matched to the TEMPO 3:4 trial population predicts a delay of 5 years to mean age of ESRD onset compared with natural disease progression, and that subgroup analysis suggests delays of 6.6 years for CKD stage 1, 4.7 years for CKD stage 2 and 2.7 years for CKD stage 3. The Committee considered that treatment given at CKD stage 1 would provide the most benefit of delayed ESRD, and that long-term benefit is dependent on a particular patient's disease status at baseline and trajectory of disease progression.

10.25. The Committee noted the treatment paradigm and dosing schedule proposed by the supplier for tolvaptan treatment would require considerable input from primary care, and there is a need to monitor patients for hepatic adverse effects.

10.26. The Committee considered that funding treatment with tolvaptan may improve equity of access to treatment for ADPKD, noting that there are challenges with patient access to dialysis e.g. lack of cultural and individual considerations with the needs of Māori, or transplant e.g. kidney availability).

10.27. The Committee noted that the supplier application concentrates on the most cost-effective patient population (CKD stages 2 and 3) with a focus on those with most severe disease, which results in a conservative Cost-Utility Analysis (CUA) from the supplier. However, the Committee considered that this approach excludes patients with CKD stage 1, whose disease would progress slowly but who would benefit from an improvement in years, and thus treatment may be relatively cost-effective for them

too (subject to further analysis). The Committee also noted, however, that analysis would need to include improvements (and consequences) in blood pressure associated with slower kidney function loss, and other pathology e.g. diabetes.

10.28. The Committee noted that, under the supplier-proposed criteria, about 530 patients per year with ADPKD may be able to benefit from treatment with tolvaptan and delayed dialysis. The Committee considered that the supplier-proposed patient group is too narrow and excludes CKD stage 1 patients who may benefit, and that the access criteria should therefore align with the patient population from the clinical trial evidence. The Committee considered that PHARMAC could further investigate the number of New Zealand patients who may benefit from treatment with tolvaptan.

10.29. The Committee considered that the costs of dialysis (which would be postponed rather than not required) would generally be balanced against the cost of treatment with tolvaptan, although the rate of ADPKD progression is highly variable and some patients may have less benefit in terms of time until dialysis is required. Members considered that on average, a patient with GFR of ~45 mL per min per 1.73m^2 may benefit from delaying ESRD by 4.5 years, with a total of about 12 years on tolvaptan treatment.

10.30. The Committee considered that tolvaptan should be funded due to the high health need of this patient group and the evidence for a benefit from tolvaptan. The Committee considered that it would like to be informed of the outcome of PHARMAC's economic modelling and considered that PHARMAC may need to prioritise different subgroups. Members considered a recent study of changes in incidence and survival of ESRD due to PKD in Australia and New Zealand (Fernando et al. Popul Health Metr. 2017;15:7), transplant rates for Auckland and rates of deterioration from the REPRISE study would provide useful data for economic modelling.

11. Sevelamer carbonate for hyperphosphataemia in patients with chronic kidney disease on dialysis

Application

11.1. The Committee reviewed an application for sevelamer carbonate (Renvela) for the management of hyperphosphataemia in patients with chronic kidney disease on dialysis.

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

Recommendation

11.3. The Committee recommended that sevelamer carbonate be funded with a **low** priority for the management of hyperphosphataemia in patients with chronic kidney disease on dialysis subject to Special Authority criteria.

11.4. The Committee requested that advice be sought from the Nephrology Subcommittee regarding the Special Authority criteria; in particular, whether eligibility should be restricted by coronary artery calcification score.

Discussion

11.5. PTAC and PTAC Subcommittees may differ in the advice they provide to PHARMAC, including recommendations' priority, due to the committees' different, albeit complementary, roles, expertise, experience, and perspectives (see Section 1).

11.6. The Committee noted that PTAC and the Nephrology Subcommittee had considered an application for sevelamer hydrochloride for the management of hyperphosphataemia in patients with chronic kidney disease on dialysis in 2013 and 2014, respectively. The Committee noted that both PTAC and the Nephrology Subcommittee had recommended the application be declined, due to poor quality evidence and safety concerns, and had both recommended that a funding application for sevelamer carbonate be submitted.

11.7. The Committee noted that the application for sevelamer carbonate was first reviewed by the Nephrology Subcommittee in March 2018, at which time the Subcommittee recommended that sevelamer carbonate be funded with a medium priority.

11.8. The Committee noted that there were 2,678 patients receiving dialysis in New Zealand in 2017 (1,913 on haemodialysis and 855 on peritoneal dialysis; ANZDATA 41st Annual Report 2018). The Committee considered that between 75% and 90% of patients on dialysis are likely to be treated with phosphate binders (St Peter et al. Am J Kidney Dis. 2018;71:246-53; Lopes et al. Am J Kidney Dis. 2012;60:90-101).

11.9. The Committee noted that Māori are disproportionately affected by end-stage kidney disease. The Committee noted data indicating that Māori accounted for 30% of all patients commencing treatment for end-stage kidney disease in 2017, and that rate of haemodialysis was four-fold higher for Māori than non-Māori/non-Pacific people (ANZDATA 41st Annual Report 2018). The Committee also noted that the need for renal replacement therapy is significantly higher for Pacific People compared with non-Māori/non-Pacific people, and that the incidence of end-stage kidney disease is increasing in this population.

11.10. The Committee considered the estimates of eligible patient numbers provided by the supplier were appropriate (742 per year at 100% uptake).

11.11. The Committee noted that dialysis is the cornerstone of homeostatic electrolyte management for patients with end-stage chronic kidney disease, but that it is not very effective at removing excess phosphate.

11.12. The Committee noted hyperphosphataemia in individuals with chronic kidney disease on dialysis can be associated with cardiovascular calcification, metabolic bone disease and an increased risk of death. The Committee considered that patients with chronic kidney disease on dialysis experience significantly reduced quality of life due to comorbidities, physical impairment and a high pill burden.

11.13. The Committee considered that the key drivers of hyperphosphataemia in patients with chronic kidney disease are phosphate retention, disordered vitamin D metabolism and secondary hyperparathyroidism.

11.14. The Committee considered that the standard treatment options for individuals with CKD on dialysis who develop elevated phosphate levels are dietary restriction of phosphate and treatment with phosphate binders.

11.15. The Committee considered that there are two phosphate binding products currently funded in New Zealand: calcium carbonate (a calcium-based binder) and aluminium hydroxide. The Committee considered that there are limitations with the use of both agents, including hypercalcaemia with calcium carbonate and aluminium intoxication with aluminium hydroxide.

11.16. The Committee noted that sevelamer carbonate is an anion exchange resin that lowers serum phosphate by binding phosphorous in the gastrointestinal tract, thereby decreasing absorption.

11.17. The Committee considered that sevelamer carbonate is a buffered formulation that avoids the risk of metabolic acidosis, which can occur with sevelamer hydrochloride.

11.18. The Committee noted that there are two crossover studies that have demonstrated sevelamer carbonate and sevelamer hydrochloride to be equivalent in controlling serum phosphorous levels (Delmez et al. Clin Nephrol. 2007;68:386-91; Fan et al. Nephrol Dial Transplant. 2009;24:3794-9).

11.19. The Committee noted a meta-analysis of 25 studies that investigated sevelamer compared with calcium-based binders in a total of 4,770 individuals with stage 3–5D chronic kidney disease (Patel et al. Clin J Am Soc Nephrol. 2016;11:232-44). The Committee noted that the study reported that patients receiving sevelamer had lower all-cause mortality (RR 0.54; 95% CI 0.32 to 0.93), lower total serum cholesterol (mean difference [MD] -20.2 mg/dL; 95% CI -25.9 to -14.5 mg/dL), lower low-density lipoprotein (LDL)-cholesterol (MD -21.6 mg/dL; 95% CI -27.9 to -15.4 mg/dL), lower calcium (MD -0.4 mg/dL; 95% CI -0.6 to -0.2 mg/dL), and a reduced risk of hypercalcaemia (RR 0.30; 95% CI 0.19 to 0.48). The Committee noted that there were no significant differences between the treatment groups in serum phosphate values or cardiovascular mortality.

11.20. The Committee noted a systematic review and network meta-analysis of 28 studies that indirectly compared the effects of available phosphate binders in a total of 8,335 patients with chronic kidney disease – mineral and bone disorder (Sekercioglu et al. PLoS One. 2016;11:e0156891). The Committee noted that the study reported that there was a higher risk of mortality with calcium-based binders compared with sevelamer (network meta-analysis RR 1.89; 95% CI 1.02 to 3.50) and that treatment with calcium-based binders was associated with a non-significant increase in hospitalisation (RR 1.293; 95% CI 0.94 to 1.74).

11.21. The Committee noted a network meta-analysis of 77 trials that indirectly compared phosphate-binder strategies in a total of 12,562 patients with chronic kidney disease (Palmer et al. Am J Kidney Dis. 2016;68:691-702). The Committee noted that the study reported that, compared with calcium-based binders, sevelamer reduced all-cause mortality (OR 0.39; 95% CI 0.21 to 0.74), reduced the risk of hypercalcaemia (OR 0.14; 95% CI 0.07 to 0.29), and reduced coronary artery calcification scores (standardised mean difference -0.20; 95% CI -0.40 to -0.01).

11.22. The Committee noted a systematic review and meta-analysis of 51 trials that indirectly compared sevelamer or lanthanum with other phosphate binders in a total of 8,829 patients with chronic kidney disease (Habbous et al. Nephrol Dial Transplant. 2017;32:111-25). The Committee noted that the study reported that, compared with calcium-based binders, sevelamer non-significantly reduced the risk of all-cause mortality (RR 0.62; 95% CI 0.35 to 1.08), reduced the risk of hypercalcaemia (RR 0.27; 95% CI 0.17 to 0.42), reduced the risk of hospitalisation (RR 0.50; 95% CI 0.31 to 0.81), reduced serum calcium (MD -0.35; 95% CI -0.49 to -0.22), reduced LDL-cholesterol (MD -20.9; 95% CI -23.3 to -18.6), and reduced coronary artery calcification scores (MD -101; 95% CI -160 to -41.7).

11.23. The Committee noted a review of 104 trials that investigated the benefits and harms of phosphate binders in a total of 13,744 patients with chronic kidney disease (Ruospo et al. Cochrane Database Syst Rev. 2018;8:CD006023). The Committee noted that the review reported that, compared with calcium-based binders, sevelamer reduced the risk of all-cause mortality (RR 0.53; CI 0.30 to 0.91) and reduced the risk of hypercalcaemia (RR 0.30; CI 0.20 to 0.43).

11.24. The Committee considered that the indirect meta-analyses indicate that sevelamer may be associated with a higher risk of gastrointestinal adverse events such as constipation, compared with calcium-based binders.

11.25. The Committee considered that the meta-analyses investigating phosphate binders were limited by both the method (indirect comparison of trials) and the quality of the clinical trials included. The Committee considered that most of the trials had moderate-to-high risk of bias, with absence of or errors in allocation concealment, randomisation and blinding. The Committee also considered that variation in trial design, including treatment duration, sample size, age, dosing, base-line serum phosphate levels, type of dialysis, and adherence, further complicated valid comparison.

11.26. The Committee noted an open-label, 24-month randomised clinical trial that investigated the use of sevelamer compared with a calcium-based binder in 466 patients receiving haemodialysis (Di Iorio et al. Am J Kidney Dis. 2013;62:771-8). The Committee noted that the study reported that serum phosphate levels were lower in the sevelamer arm and that sevelamer-treated patients had lower cardiovascular mortality due to cardiac arrhythmias (HR 0.06; 95% CI 0.01 to 0.25); however, the Committee noted that coronary artery calcification scores were lower in the sevelamer arm at baseline and that overall there was lower-than-expected mortality.

11.27. The Committee noted an analysis of the Dialysis Outcomes and Practice Pattern Study data that investigated whether the initiation of sevelamer was associated with improved survival in patients on haemodialysis treated with calcium-based binders (Komaba et al. Clin J Am Soc Nephrol. 2017;12:1489-1497). The Committee noted that the study reported that patients treated with sevelamer had a 14% lower risk of mortality compared with as-yet-untreated patients (HR 0.86; 95% CI 0.76 to 0.97).

11.28. The Committee noted a cost-effectiveness analysis that compared sevelamer with calcium acetate in 4,674 dialysis patients in South Korea (Cho et al. Clin Ther. 2018;40:123-34). The Committee noted that the authors of this study concluded that the higher cost of sevelamer was adequately offset by improved survival. However, the Committee considered that the survival benefit may have been overestimated in this study, and that it was unclear how relevant the results were to the New Zealand clinical setting.

11.29. The Committee noted that there are no studies comparing sevelamer carbonate with aluminium hydroxide, but considered that this is of limited relevance, as the use of long-term aluminium hydroxide is not recommended due to toxicity.

11.30. The Committee noted that there are limited quality of life data available for sevelamer carbonate.

11.31. The Committee considered that if sevelamer carbonate was funded, there may be some additional health care costs associated with the treatment of constipation and pruritus.

11.32. The Committee considered that there are some signals that treatment with sevelamer is associated with reduced all-cause mortality, but that it is unclear whether this is due to the agent itself reducing the risk of death, or whether there is an increased risk of all-cause mortality associated with calcium-based binders (as study comparators), or both.

11.33. The Committee considered that sevelamer carbonate would likely be used as an add-on therapy to calcium-based binders in some patients, which generates additional uncertainly about cardiovascular benefits, given it is unclear whether calcium-based binders could instead be causing cardiovascular harm.

11.34. The Committee considered that there is weak and low-quality evidence that sevelamer carbonate is as effective as calcium-based binders for managing hyperphosphataemia, that it reduces the risk of hypercalcaemia compared with

calcium-based binders, and that it lowers total/LDL cholesterol. The Committee noted that the use of sevelamer carbonate may also be associated with a reduction in all-cause mortality, but considered that the evidence for this is of poor quality.

11.35. The Committee noted the Special Authority criteria proposed by the Nephrology Subcommittee, but considered that the inclusion of a high coronary artery calcification score could be of value in identifying the patients at greatest need of an alternative to calcium-based binders. The Committee requested that further advice be sought from the Nephrology Subcommittee on this point.

12. Budesonide for the treatment of mild to moderate ulcerative colitis

Application

12.1. The Committee reviewed the application for budesonide colonic release (CR) 9 mg for the treatment of mild to moderate ulcerative colitis from Pharmaco (NZ) Ltd.

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 budesonide colonic release (CR) 9 mg for the treatment of mild to moderate ulcerative colitis be funded with a low priority, noting a small health benefit in patients who are unable to tolerate prednisone due to adverse effects, subject to the following Special Authority criteria:

Special Authority for Subsidy
Initial application – (ulcerative colitis) from any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. Patient has histologically confirmed left-sided or proctosigmoidal ulcerative colitis; and
2. Patient is aged 18 years or older; and
3. Patient has a Simple Clinical Colitis Activity Index (SCCAI) score of between 5 and 11; and
4. Patient has had an inadequate response following optimised therapy with 5-aminosalicylates; and
5. Any of the following:
    5.1. Diabetes; or
    5.2. Cushingoid habitus; or
    5.3. Osteoporosis where there is significant risk of fracture; or
    5.4. Severe acne following treatment with conventional corticosteroid therapy; or
    5.5. History of severe psychiatric problems associated with corticosteroid treatment; or
    5.6. History of major mental illness (such as bipolar affective disorder) where the risk of conventional corticosteroid treatment causing relapse is considered to be high; or
    5.7. Relapse during pregnancy (where conventional corticosteroids are considered to be contraindicated)
6. Budesonide colonic release 9 mg tablets to be administered once daily for up to 8 weeks.

Renewal from any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:
1. Treatment remains appropriate and the patient is benefiting from treatment; and
2. Budesonide colonic release 9 mg tablets to be administered once daily for up to 8 weeks; and
3. Patient can receive a maximum of two 8-week treatment cycles with budesonide colonic release 9 mg tablets within a 12-month period.

Background

12.4. The Committee noted that in October 2018 the Gastrointestinal Subcommittee reviewed the application for budesonide colonic release (CR) 9 mg and the Subcommittee recommended that budesonide CR 9 mg for the treatment of mild to moderate ulcerative colitis be funded with a medium priority, subject to Special Authority criteria.

12.5. The Committee noted that in February 2019 PTAC reviewed the record from the October 2018 Gastrointestinal Subcommittee meeting, and PTAC did not accept the recommendations from the Subcommittee regarding budesonide CR 9 mg and requested that the Committee review a paper on budesonide CR 9 mg. The Committee noted that in February 2019 PTAC had concerns about what PTAC considered were the proposal's modest reworking of the formulation, poor quality evidence, lack of clarity around an appropriate comparator for New Zealand, main benefit (likely to be avoidance of steroid side-effects) and likely high cost.

Discussion

12.6. The Committee noted that the health need of patients with mild to moderate ulcerative colitis (UC) has been described in the previous Gastrointestinal Subcommittee and PTAC records. The Committee considered that UC is a long-term disease with a variable prognosis including relapses and remissions, and noted that UC reduces the quality of life of New Zealand patients with major impact in many areas (Crohn's Colitis New Zealand [CCNZ], 2017).

12.7. The Committee noted that New Zealand patients with UC initially receive funded treatment with systemic or local 5-ASAs e.g. mesalazine, olsalazine or sulphasalazine; if these agents are insufficient, then oral steroids e.g. prednisone or hydrocortisone; are used, followed by immunosuppressants e.g. azathioprine or methotrexate, and then biologics for severe UC e.g. infliximab or adalimumab. The Committee noted that treatment with prednisone, even in other indications, is known to be associated with a predictable corticosteroid-related side effects in a proportion of patients (Manns et al. Gastroenterology. 2010:139;1198-206).

12.8. The Committee considered that patients had better disease course long-term through actively managing disease flare ups. Members considered that while treatment of relapse is beneficial, most patients would require other treatments in time. The Committee considered that up to 25% of patients whose disease progresses require a colectomy within 10 years and 12-14% patients develop extra-intestinal disease.

12.9. The Committee noted that budesonide colonic release (CR) 9 mg is a specific formulation of budesonide, a second-generation glucocorticoid that is significantly more potent than prednisone, with a different mechanism of absorption as described in the Gastrointestinal Subcommittee record. The Committee considered that while budesonide CR 9 mg largely acts locally, it still has systemic effects.

12.10. The Committee noted that budesonide CR 9 mg is approved by Medsafe and internationally (and is funded in about half of countries where it is approved) for the induction of remission in adult patients with mild to moderate active UC where 5-ASA therapy has been not sufficient or not tolerated.

12.11. The Committee considered that the current funding application specifically seeks funding of the CR formulation of budesonide and considered that the CR delivery was different but results in the same plasma concentration of budesonide and has a systemic effect. The Committee considered that the appropriate New Zealand comparator treatment for budesonide CR 9 mg would be prednisone, which is used as the standard of care treatment of mild to moderate UC that is not controlled by 5-ASA drugs.

12.12. The Committee noted that budesonide controlled ileal release (CIR) 3 mg (Entocort CIR) is currently funded, with use restricted to Crohn's disease, microscopic colitis or gut Graft vs Host disease, and considered that budesonide CIR is used as a 9 mg dose with a similar treatment effect to prednisone 40 mg. Members noted that the Gastrointestinal Subcommittee had concerns about the side effect profile of prednisone, and considered that budesonide CIR is used for patients with Crohn's

disease especially in those unable to take or tolerate prednisone (~25% of patients with Crohn's disease). Members considered that an alternative to prednisone for patients with UC may be useful.

Evidence

12.13. The Committee noted that the results of three randomised, double-blind, placebo-controlled clinical trials have been described in the Gastrointestinal Subcommittee record (CORE I, Sandborn et al. Gastroenterology. 2012;143:1218-1226; CORE II Travis et al. Gut. 2014;63:433-41; and CONTRIBUTE Rubin et al. J Crohns Colitis. 2017;11:785-791).

12.14. The Committee considered that the CORE I trial (with mesalamine [5-ASA] comparator) and CORE II trial (with budesonide CIR [Entocort] 9 mg comparator) were similar studies, both having endoscopic and clinical remission endpoints. The Committee considered that these studies were not powered to assess clinical improvement, which the Gastrointestinal Subcommittee considered was the most important endpoint for patients with mild to moderate UC. The Committee noted that the CONTRIBUTE trial included clinical improvement as an exploratory endpoint, did not include any safety endpoints, and considered that the CONTRIBUTE trial criteria excluded patients less likely to respond to treatment.

12.15. The Committee noted that the rate of combined clinical and endoscopic remission (CER) reported in CORE I was 17.9% with budesonide CR 9 mg compared to 7.4% with placebo, and the CER reported in CORE II was 17.4% with budesonide CR 9 mg compared to 4.5% with placebo. The Committee also noted that the rate of CER reported in CONTRIBUTE was 13% with budesonide CR 9 mg compared to 7.5% with placebo. The Committee noted clinical improvement (an important clinical endpoint) was not different between the budesonide 9 mg and placebo groups in the CORE I study, and clinical improvement was not different between budesonide and placebo in the CORE II study.

12.16. The Committee considered that the CORE II results for combined clinical and endoscopic remission (CER) were similar between budesonide CR 9 mg (17.4%) and budesonide CIR (Entocort) 9 mg (12.6%) although the trial was not statistically powered for this comparison.

12.17. The Committee noted the results of a pooled analysis of 5 clinical trials (including CORE I, CORE II, and others) and considered that the incidence of severe adverse events (AEs) and glucocorticoid AEs were similar across studies, and noted that glucocorticoid AEs occurred in less than 10% of patients (Lichtenstein et al. J Crohns Colitis. 2015;9:738-746). The Committee considered that the CORE I and CORE II trials were not designed to demonstrate a reduction in side effects.

12.18. The Committee noted the results of a Cochrane systematic review of oral budesonide for induction of remission in UC (Sherlock et al. Cochrane Database Syst Rev. 2015: Art. No. CD007698), which reported that the evidence for clinical improvement and AEs was of low to moderate quality according to GRADE analysis. The Committee considered that the results suggest budesonide CR 9 mg is effective but offers no additional benefit than other standard of care treatments.

12.19. The Committee noted that the clinical trials that provide the evidence for budesonide CR 9 mg did not include New Zealand participants. The Committee also noted that the clinical trials did not investigate or were not powered sufficiently to assess primary endpoints that are most clinically relevant in New Zealand (i.e. clinical improvement).

12.20. The Committee noted that there are no clinical trials that directly compare the budesonide CR 9 mg formulation against prednisone, which would be the appropriate

comparator for New Zealand and internationally. The Committee considered that the small clinical trial of budesonide 10 mg compared to prednisone 40 mg (Löfberg et al. Gastroenterology. 1996:110;1713-8) was not relevant due to use of a different budesonide formulation than this funding application's.

12.21. The Committee considered that the benefit of budesonide CR 9 mg compared to prednisone would be small, since prednisone already provides a health benefit over placebo. The Committee considered that further clinical trial data addressing this information gap was unlikely to be forthcoming. The Committee considered that the evidence does not suggest that there is a particular patient subgroup that would receive the most benefit from treatment with budesonide CR 9 mg.

General

12.22. The Committee noted that the proposed price of budesonide CR 9 mg was significantly higher than that of prednisone.

12.23. The Committee noted that the Gastrointestinal Subcommittee estimated that less than 3,000 patients each year may meet the Subcommittee's proposed Special Authority criteria for treatment with budesonide CR 9 mg.

12.24. The Committee considered that the Special Authority criteria proposed by the Gastrointestinal Subcommittee excludes patients for whom 5-ASA drugs are ineffective or not tolerated, but considered it appropriate that these patients access budesonide CR 9 mg. The Committee noted that the Simple Clinical Colitis Activity Index (SCCAI) scores require clinical assessment and considered that this introduced some subjectivity with inter-rater and test-retest variability in assessments, affecting validity. Members considered that the reason for a limited treatment duration of 16 weeks in the Special Authority (initial and renewal) was unclear.

12.25. The Committee considered that its view of the available evidence was less favourable than that of the Gastrointestinal Subcommittee and that budesonide CR 9 mg would provide only a small health benefit in patients who are unable to tolerate prednisone due to adverse effects; however, the Committee was supportive of funding budesonide CR 9 mg with a low priority.