Record of the Nephrology Advisory Committee Meeting held on 17 March 2023

Nephrology Advisory Committee records are published in accordance with the Terms of Reference for the Specialist Advisory Committees 2021.

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

The Nephrology Advisory Committee may:

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

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

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

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

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

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

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

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1. Attendance

Present
Elizabeth Dennett - Chair
Bruce King
Caroline Chembo
Kannaiyan Rabindranath
Nick Cross
William Wong

Apologies
Colin Hutchison

2. Summary of recommendations

Pharmaceutical and Indication	Recommendation
• Lanthanum carbonate for adults with chronic kidney disease (CKD) with hyperphosphataemia not adequately controlled on calcium	Medium Priority
• Sevelamer carbonate for adults with chronic kidney disease (CKD) with hyperphosphataemia not adequately controlled on calcium	Specific coronary artery calcification score not be included in the Special Authority criteria
• Eculizumab for the treatment of atypical Haemolytic Uraemic Syndrome (aHUS) in adults and children	Low Priority
• Rituximab for the treatment of Class III and IV active lupus nephritis as part of the induction phase of therapy	Declined

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

3.1. This meeting record of the Nephrology Advisory Committee is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) 2021 and Specialist Advisory Committees 2021.Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of Specialist Advisory Committees and PTAC.

3.2. Conflicts of Interest are described and managed in accordance with section 6.4 of the SAC Terms of Reference.

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

Pharmac considers the recommendations provided by both the Nephrology Advisory Committee and PTAC and any other relevant Specialist Advisory Committees when assessing applications for treatments for the Nephrology Therapeutic Group.

4. Welcome and introduction

4.1. The Chair welcomed members to the meeting. Members and Pharmac staff introduced themselves. This meeting was held via a combination of zoom and in-person for Committee members and Pharmac staff.

5. Record of Nephrology Subcommittee meeting held Tuesday, March 20, 2018

5.1. The Advisory Committee reviewed the minutes of the Nephrology Subcommittee meeting held on 20 March 2018 and agreed that the minutes be accepted.

6. Correspondence and Matters Arising

Tacrolimus (for nephrotic syndrome)

6.1. The Committee noted the current Special Authority criteria for tacrolimus in the treatment of non-transplant indications and the requirement to trial and discontinue ciclosporin either due to side effects or inadequate clinical response. The Committee noted that approximately 50 patients access tacrolimus for non-transplant indications each year.

6.2. The Committee considered that a reasonable proportion of between 25% to 50% of people accessing tacrolimus for non-transplant indications would be for nephrotic syndrome. The Committee noted that adults are typically administered doses of 3mg to 4mg twice daily and considered patients are treated for at least one year and may remain on treatment long term.

6.3. The Committee noted that dosing on either ciclosporin or tacrolimus is according to blood levels and requires laboratory dose monitoring with decreasing frequency (twice a week, then monthly, then biannually). The Committee considered that people with nephrotic syndrome treated with ciclosporin are often only treated for 3 months and then switched to tacrolimus due to side effects. The Committee noted that tolerability issues with ciclosporin are more common with paediatric populations than in adults. The Committee considered that if the requirement to trial ciclosporin before tacrolimus was removed, then savings to the health system may be generated from reduced laboratory testing as frequent initial blood monitoring would only be required once as patients are initiated on to tacrolimus and not ciclosporin and then tacrolimus.

6.4. The Committee noted it was in favour of Pharmac removing the requirement to trial ciclosporin in the non-transplant setting and considered this would result in minimal incremental cost to the Combined Pharmaceutical Budget and potential cost savings to the health system.

Indomethacin update for the Committee

6.5. The Committee noted that the supplier of indomethacin in the community and hospital setting had been discontinued and that Pharmac were unable to find a Medsafe approved product. The Committee noted that indomethacin capsules/injection/suppositories remain listed in section H of the schedule for use in the Hospital setting as an “any brand” listing. however, in the community setting no funded indomethacin was available.

6.6. The Committee noted in the past two years six Named Patient Pharmaceutical Assessment (NPPA) applications had been received by Pharmac for the treatment of congenital nephrotic syndrome. The Committee noted that the NPPA process for indomethacin was established, however it considered whether the administrative process of accessing for congenital nephrotic syndrome could be alleviated by listing indomethacin in the community schedule. The meeting noted the long-term listing of medicines under section 29 is not typically recommended, particularly by Medsafe, and listing of medicines under section 29 is usually reserved for the purpose of a short-term listing to manage a supply interruption. The Committee considered that the need to list indomethacin on the community schedule wasn't significant and that the current access mechanism for indomethacin through NPPA is established and allows access for the small number of patients presenting with congenital nephrotic syndrome. The Committee noted this also applied to NPPA applications for dipyridamole which is applied for in combination with indomethacin.

Mupirocin 2% ointment

6.7. The Committee noted a request from a clinician at Starship Hospital to fully fund mupirocin ointment, which is used routinely to prevent exit site infections for paediatric patients undergoing peritoneal dialysis. The meeting noted that currently mupirocin 2% ointment is only part-funded and comes with a 'part-charge' of $4.90 per tube, which comes as a significant barrier to access for some patients, in particular Māori and Pacific people at increased risk of requiring peritoneal dialysis treatment. The Committee noted that poor access and use of mupirocin ointment could result in the development of complications such as peritonitis.

6.8. The Committee noted there are available funded alternatives including hydrogen peroxide, povidone iodine, sodium fusidate and sulfadiazine silver cream. However, the Committee considered that treatment with preventative antibacterial topical preparations for peritoneal dialysis patients is long term and funded alternatives such as hydrogen peroxide, povidone iodine and sulfadiazine silver may not be suitable due to skin irritation or allergic reaction. The Committee considered that there was no strong evidence demonstrating differential effectiveness of topical antibacterials and that the appropriate comparator for mupirocin ointment is topical sodium fusidate. The Committee considered that an appropriate target group for fully funding mupirocin ointment would include peritoneal dialysis patients and patients with long term catheter or injection emplacements with increased risk of exit site infections. The Committee recommended seeking advice from the Anti-infective Advisory Committee as to the comparative evidence of topical mupirocin and sodium fusidate.

Potassium chloride effervescent tablets

6.9. The meeting noted, in the paediatric context, available potassium chloride treatment options are not suitable as they are either difficult to administer or contain a number of additional compounds, such as potassium bicarbonate and potassium carbonate which are difficult to prescribe for infants that require potassium supplementation. The meeting noted that there is a potassium chloride solution (2mmol/ml potassium) available in the hospital setting that should be considered in a future meeting for funding in the community.

Potassium citrate tablets

6.10. The meeting noted the current Special Authority access criteria for potassium citrate and the requirement for eligible patients to have had more than two renal calculi in the previous two years. The meeting requested a future discussion over the appropriateness of this criterion.

6.11. The meeting noted there is an ongoing clinical need for potassium citrate in a tablet form, due to suitability issues in relation to the currently funded oral liquid formulation which impacts adherence to lifelong treatment. The meeting considered that if a tablet form of potassium citrate was available, patient switching from the liquid to the tablet formulation would be high except for younger patients unable to swallow tablets.

Epoetin alfa for congenital nephrotic syndrome

6.12. The meeting noted there have been 3 NPPA applications for anaemia associated with congenital nephrotic syndrome (CNS) over the last 5 years. The committee considered whether an addition to the current Special Authority access criteria for epoetin alfa would be useful for meeting the clinical needs of this patient group. The Committee considered, due to the low number of NPPA applications, widening the access criteria for people with anaemia associated with CNS was not necessary, as patients are adequately treated via NPPA currently.

Epoetin alfa – amending prescriber restrictions for Special Authority applications.

6.13. The meeting noted Pharmac had received a request from Nephrology Nurse Practitioners New Zealand to widen access within the special authority criteria for epoetin alfa to allow Nephrology Nurse Practitioners to initiate treatment. The Committee noted the following potential benefits of enabling Nephrology Nurse Practitioners to apply for special authority, increased access to treatment, reduced delays in commencing treatment, decreased need for blood transfusions, support established, and effective Nurse led models of care and minimisation of waste through appropriate and timely prescribing.

6.14. The Committee considered there is a role for Nephrology Nurse Practitioners in the prescribing of epoetin alfa to treat chronic renal failure and associated anaemia. The Committee considered there was also a role for Nurse Practitioners in other clinical contexts. The meeting considered it was unclear what specific accreditation, if at all, would be needed to allow appropriate Nurse Practitioners to apply for special authority. The Committee considered that, although supportive of Pharmac expanding the prescriber eligibility for epoetin alfa, there needed to be a wider consideration by Pharmac as to how relevant Nurse Practitioners and Nurse prescribers can be inserted into all appropriate special authorities and necessary steps to implement appropriately.

Cinacalcet

6.15. The Committee noted Pharmac's decision to widen access to cinacalcet from 1 December 2022 for people with primary, secondary, and tertiary hyperparathyroidism. The Committee considered whether there remained an unmet health need for people post kidney transplant and for people with hyperparathyroidism for whom surgery is possible.

6.16. The Committee considered there would be very few patients requiring ongoing cinacalcet post kidney transplant. The Committee considered that most patients post kidney transplant, in addition to normalised renal function, would also experience corrected hyperparathyroidism and that the 12-week cinacalcet free treatment interval was a reasonable length of time for these clinical outcomes to be demonstrated and that the clinical risk in this timeframe would be extremely low. The Committee also considered that in order to be eligible for a kidney transplant, people with hyperparathyroidism would require their parathyroid hormone levels to be addressed either medically or surgically, which the current access criteria addressed, and that practically a clinician concerned with stopping cinacalcet immediately post kidney

transplant could continue treatment with cinacalcet before beginning a treatment free period of 12 weeks. The Committee noted, based on the current Special Authority criteria for cinacalcet in the treatment of hyperparathyroidism, that they did not consider there to be an unmet health need for patients post kidney transplant.

6.17. The Committee did not consider there to be an unmet health need for people with hyperparathyroidism eligible for surgery. However, the Committee considered that cinacalcet use is likely to increase substantially over time as clinicians opt to treat people with hyperparathyroidism with cinacalcet who may be eligible for surgery. The Committee considered this is likely due to the invasive nature of parathyroidectomy, surgery wait times and avoidance of complications from surgery.

Levamisole for nephrotic syndrome

6.18. The Committee considered that there remained a role for levamisole in the treatment of people with frequently relapsing steroid sensitive nephrotic syndrome, with the highest health need being in children. The Committee noted levamisole is sparsely used worldwide and has led Pharmac being unable to source a reliable product for use in New Zealand. The Committee noted that levamisole is used regularly in veterinary space as an anthelminthic. The Committee noted that until an appropriate levamisole product could be identified and sourced by Pharmac the application could not be considered further.

7. Nephrology Pharmaceutical and NPPA Review

Update on Funding Decisions

7.1. The Committee noted that tolvaptan was listed on the schedule in December 2022 for the treatment of autosomal dominant polycystic kidney disease (ASDKD) subject to special authority criteria.

7.2. The Committee noted that widening access to cinacalcet for the treatment of primary, secondary and tertiary hyperparathyroidism subject to Special Authority criteria was funded from December 2022.

7.3. The Committee noted that widening access to rituximab for the treatment of membranous nephropathy subject to Special Authority criteria was funded from March 2021.

7.4. The Committee noted that sirolimus was listed on the schedule in February 2021 for the treatment of tuberous sclerosis related renal angiomyolipomata subject to Special Authority criteria. The Committee considered that the current Special Authority criteria was appropriate in meeting the greatest health need in people living with tuberous sclerosis related angiomyolipomata.

Sodium-glucose cotransporter 2 inhibitors (SGLT2)

7.5. The Committee noted two letters received by Pharmac, one from Kidney Health New Zealand and another from Nephrologists working at Te Whatu Ora Health New Zealand requesting changes to the current Special Authority criteria for SGLT2 inhibitors. The Committee noted the proposed changes in the letters included removal of the HbA1c criteria and widening access to include people living with non-diabetic chronic kidney disease.

7.6. The Committee noted that a fulsome review of the evidence is necessary for the range of patient populations likely to benefit from SGLT2 inhibitors, including non-diabetic patients with renal disease and non-diabetic patients with cardiac disease.

7.7. The Committee noted most important developments in renal disease management in recent times and that the evidence supporting this was of high quality.

7.8. The Committee recommended to Pharmac to encourage a formal application to be submitted by either the supplier and/or Nephrologists. The Committee considered that an application received by Pharmac in the first instance, was reasonable to be reviewed by PTAC with follow up advice from the Nephrology Advisory Committee.

New Funding applications received by Pharmac

Belimumab

7.9. The Committee noted that Pharmac had received an application from the supplier for belimumab for the treatment of active lupus nephritis as an add on to standard of care. The Committee noted that the application was received close to the date of the March 2023 meeting and that the subcutaneous formulation in the application is awaiting Medsafe submission.

7.10. The Committee noted the superior suitability of a subcutaneous injection formulation of belimumab that can be self-administered over intravenous administration.

7.11. The Committee noted the unmet health need in lupus nephritis, particularly in the induction phase of treatment and that biologic treatment with rituximab was only available in the relapsed/refractory setting.

7.12. The Committee considered the proposed Special Authority criteria and recommended the removal of any age-based criteria. The Committee noted they were not aware of any clinical trials in children or adolescents under the age of 18 years but considered that restricting access to people 18 years of age or older was not appropriate as there is no evidence to suggest people younger than 18 years of age would not benefit from treatment with belimumab.

Ramipril transition

7.13. The Committee noted that early data on ramipril usage is not adequate to determine long-term patient uptake but noted that cilazapril usage has been declining since the 2020/21 financial year and angiotensin II inhibitor drug use had been increasing over the same period. The Committee noted that cilazapril supply is due to run out by the end of 2023 and that Pharmac would need to be active in their communication with General Practitioners, Nephrologists, Cardiologists and Pharmacists around the delisting of cilazapril and switching patients to alternative agents.

General items, agents of interest and therapeutic developments in nephrology

7.14. The Committee noted it would be useful to analyse the trends of use for medicines used in nephrology to determine under or overuse of particular pharmaceuticals. The Committee noted it would be useful for Pharmac to provide this data in future meetings.

7.15. The Committee noted that there was an unmet health need for adults with nephrotic syndrome not currently met by the rituximab Special Authority criteria.

7.16. The Committee considered that Pharmac could expect funding applications in the future for:

- voclosporin for lupus nephropathy;
- tolvaptan for hypernatremia;
- budesonide for IgA nephropathy; and
- a single-molecule, dual endothelin, and angiotensin receptor antagonist (sparsentan) for IgA nephropathy.

7.17. The Committee noted that there are therapeutic developments in oral epoetin alfa treatments internationally that have shown to be effective.

7.18. The Committee noted that there are therapeutic developments for uremic pruritus treatment with clinical evidence emerging for an intravenous opioid mu receptor antagonist.

8. Lanthanum carbonate and sevelamer carbonate for adults with chronic kidney disease (CKD) with hyperphosphataemia not adequately controlled on calcium

Application

8.1. The Advisory Committee reviewed the supplier application for lanthanum carbonate (Fosrenal) in the community and hospital for the treatment of hyperphosphatemia experienced by adult individuals who have been diagnosed with chronic kidney disease (CKD) who are receiving dialysis and whose phosphate serum levels are not adequately controlled with calcium carbonate.

8.2. The Advisory Committee noted that advice was also sought on the proposed Special Authority criteria and the use of coronary artery calcification scores following a 2019 PTAC review of an application from a supplier for the use of sevelamer carbonate to manage hyperphosphataemia in individuals diagnosed with CKD and who are on dialysis.

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

Recommendation

8.4. The Advisory Committee **recommended** that lanthanum carbonate be listed with a **medium priority** within the context of treatment of renal disease and subject to the following Special Authority criteria:

> LANTHANUM CARBONATE
> **Initial application** – Lanthanum carbonate in hyperphosphataemia
> Applications only from a relevant specialist or any prescriber on the recommendation of a relevant specialist. Approvals valid for 12 months.
> Prerequisites (tick boxes where appropriate):
> 1. Patient has hyperphosphataemia; and
> 2. Patient has significant renal disease and
> 3. Either
> 3.1. Patient is currently taking a calcium-based binder or
> 3.2. Patient has trialled at least one-phosphate reducing agent and not experienced adequate reduction of phosphate or has experienced intolerable toxicity; and
> 4. Patient's calcium-phosphate product is at least $4.5mmol^2/L^2$
>
> **Renewal applications**
> Applications only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months.
> 1. Treatment remains clinically appropriate

8.5. In making this recommendation, the Committee considered:

8.5.1. The unmet health need for individuals with CKD whose phosphate is not currently adequately controlled using funded treatment options.

8.5.2. The known negative effects of elevated calcium and phosphate in individuals with CKD.

8.5.3. That although there is a lack of evidence with regard to clinical outcomes, another agent is necessary for controlling phosphate levels.

8.5.4. That international guidelines recommend the use of non-calcium-based binding agents for some individuals with CKD.

8.6. The Advisory Committee **recommended** that the Special Authority criteria for sevelamer carbonate be aligned with that of lanthanum carbonate, and that the requirement for a specific coronary artery calcification score not be included in the criteria.

8.6.1. The Advisory Committee considered that this was an unnecessarily restrictive measure which would not aid in the identification of those with the greatest need.

Discussion

Māori impact

8.7. The Committee discussed the impact of funding lanthanum carbonate and sevelamer carbonate for the treatment of hyperphosphataemia on Māori health areas of focus and Māori health outcomes. The Committee noted that there are inequities in the incidence and prevalence of kidney failure, and treatment practices in kidney replacement therapy for Māori compared to non-Māori, non-Pacific people population in New Zealand. The Committee noted that Māori have a substantially higher rate of type 2 diabetic nephropathy causing kidney failure, and are significantly less likely to receive a kidney transplant, and more likely to initiate dialysis with haemodialysis, Māori are provided with facility-based dialysis as the principal modality of care, with a lower provision of home-based modalities compared with non-Māori, non-Pacific peoples (Australia and New Zealand Dialysis and Transplant Registry. 44th Annual Report.2021). The Committee noted that Māori also have significantly lower rates of kidney transplantation prior to requiring dialysis. The Committee noted that there is no direct evidence of differences in hyperphosphataemia between ethnicities.

Background

8.8. The Committee noted that an application for lanthanum carbonate for the treatment of hyperphosphataemia experienced by adult individuals who have been diagnosed with CKD, receiving dialysis and whose phosphate serum levels cannot be controlled on calcium carbonate was previously reviewed by PTAC in November 2021 where PTAC recommended the application be declined and considered that the evidence available at the time was consistent with only a modest clinically meaningful health benefit, with some difficulty in translating this into the New Zealand setting, and the high-quality evidence demonstrates no benefit of lanthanum carbonate over calcium carbonate. The Committee noted that PTAC requested advice from the Nephrology Advisory Committee regarding the health benefit of lanthanum carbonate versus sevelamer carbonate, and whether there is a subgroup of individuals who would benefit from lanthanum carbonate, such as those contraindicated to using, or refractory to, calcium carbonate, including patient number estimates for this population.

8.9. The Committee noted that an application for sevelamer carbonate for the treatment of hyperphosphataemia experienced by adult individuals who have been diagnosed with chronic kidney disease and are receiving dialysis has previously been discussed by the Nephrology Subcommittee (now the Nephrology Advisory Committee) in 2018. The Committee noted that, in 2018, it recommended that sevelamer carbonate to be listed with a medium priority on the Pharmaceutical Schedule for individuals who are on dialysis and expected to be on dialysis for at least 12-months, currently taking a calcium-based binding agent and with a phosphate level equal or greater than 4.5 mmol/L[2].

8.10. The Committee noted that, in 2019, PTAC recommended that sevelamer carbonate be funded with a low priority for the management of hyperphosphataemia in people with chronic kidney disease on dialysis subject to Special Authority criteria. The

Committee noted that, at that time PTAC requested that advice be sought from the Nephrology Advisory Committee regarding the Special Authority criteria, in particular whether eligibility should include CT coronary artery calcification (CAC) scores to identify those at greatest need.

Health Need

8.11. The Committee noted that hyperphosphatemia describes an individual's measured serum phosphate levels being greater than 4.5mg/dL (1.46mol/L). The Committee noted that daily phosphate load is largely excreted by the kidneys; therefore, hyperphosphatemia occurs when renal function is impaired to the extent that reduced renal phosphate excretion and other homeostatic mechanisms fail to eliminate the excess phosphate. The Committee noted that hyperphosphatemia in CKD is associated with cardiovascular calcification, metabolic bone disease and the development of secondary hyperparathyroidism.

8.12. The Committee noted that dialysis commonly inadequately controls serum phosphorus. The Committee noted that individuals on dialysis are often treated with phosphate-binding agents.

8.13. The Committee noted that the currently available treatment for hyperphosphataemia secondary to CKD are calcium carbonate and aluminium hydroxide. The Committee noted that individuals with progressive CKD are treated with phosphate binders before they reach dialysis. The Committee noted that a minority of individuals receiving treatment with aluminium hydroxide for hyperphosphataemia would experience some adverse events and toxicity and considered that this would not be common. The Committee also noted that aluminium is partially absorbed by the body and is excreted through the kidneys, leading to a higher risk of aluminium accumulation in the kidneys of individuals with CKD, compared to lanthanum which is very poorly absorbed and not excreted by the kidneys. The Committee noted that children with hyperphosphatemia and hyperparathyroidism are contradicted to aluminium due to the toxicity risks and the impact on the brain and skeleton.

8.14. The Committee noted that in 2021, there were approximately 3155 New Zealanders on dialysis, 75-90% of which would be using phosphate binders. Hence, the Committee considered that approximately 2500-2850 individuals on dialysis would be receiving medical treatment for hyperphosphataemia annually. The Committee considered that if those with CKD not yet on dialysis are taken into consideration, this number could be potentially two to three times higher. The Committee note that there is no data relating to how well current treatments for hyperphosphataemia are working, or how many individuals with hyperphosphataemia who are taking currently funded treatments still do not have adequately controlled phosphate levels.

8.15. The Committee noted that the applications being assessed were targeted to individuals who require treatment for hyperphosphataemia who are on dialysis but considered that this should be expanded to include all individuals with CKD requiring treatment for hyperphosphataemia. The Committee considered that the benefits/harms of phosphate binders are likely to be the same between these two groups.

Health Benefit

8.16. The Committee noted that lanthanum carbonate is a non-aluminium, non-calcium-based phosphate binder, which forms insoluble lanthanum phosphate complexes that pass through the gastrointestinal tract unabsorbed, reducing phosphate absorption. The Committee noted that sevelamer carbonate is an anion exchanged resin which lowers the phosphate concentration in serum by binding phosphorous in the gastrointestinal tract and decreasing absorption and does not contain calcium.

8.17. The Committee noted the NICE 2021 guideline for the assessment and management for chronic kidney disease (NG203) which compared all phosphate binders, which included a network metanalysis. The Committee noted that this guideline discussed and interpreted the evidence and made recommendations for a combined population of individuals with stage 5 CKD on dialysis and stage 4 or 5 CKD not on dialysis. The Committee noted that this guidance document commented on the lack of credible mortality data available.

8.18. The Committee noted that the network meta-analysis presented in NG203 compared eleven different treatments, including those currently funded in New Zealand, lanthanum carbonate and sevelamer carbonate. The Committee noted that there was not a clinically significant difference between any of the agents in reducing phosphate levels, and that treatments varied in their efficacy at different time points. The Committee considered the quality of evidence included in the network meta-analysis to be of low quality.

8.19. The Committee noted that calcium carbonate treatment increases calcium in the blood, but considered that this is not necessarily harmful to individuals receiving treatment unless calcium levels are already high (i.e. hypercalcaemia). The Committee noted that in this instance, calcium containing binders would likely not be used.

8.20. The Committee note the LANDMARK trial (Ogata et al. JAMA. 2021; 18:1946-1954) where individuals with CKD, hyperphosphatasaemia and at least one factor of vascular calcification were randomised to receive either lanthanum carbonate (n = 1154) or calcium carbonate (n = 1155) and titrated to achieve serum phosphate levels of between 3.5 mg/dL and 6.0 mg/dL. The primary outcome was a composite cardiovascular event (cardiovascular death, nonfatal myocardial infarction or stroke, unstable angina, transient ischemic attack, or hospitalization for heart failure or ventricular arrhythmia). Following 3.16 years cardiovascular events occurred in 147 of 1063 patients in the lanthanum calcium group and 134 of 1072 patients in the calcium carbonate group (incidence rate, 4.80 vs 4.30 per 100 person-years; difference 0.50 per 100 person-years [95% CI, -0.57 to 1.56]; hazard ratio [HR], 1.11 [95%, CI, 0.88 to 1.41], P = 0.37). There were no significant differences in all-cause death (difference, 0.43 per 100 person-years [95% CI, -0.63 to 1.49]; HR, 1.10 [95% CI, 0.88 to 1.37]; P = 0.42).

8.21. The Committee considered that the available evidence does not suggest lanthanum is likely to significantly reduce mortality or the number of cardiovascular events. The Committee considered that mortality, quality of life, cardiovascular morbidity, and vascular calcification outcomes are clinically important to consider for individuals with CKD but considered that there is no strong evidence to inform how and to what degree this is impacted by lowering phosphate. However, the Committee considered that lowering phosphate was clinically desirable and that lanthanum would be a useful additional option for clinicians.

8.22. The Committee noted that the context of the applications for lanthanum carbonate and sevelamer carbonate was to include these agents as alternatives to current treatments and not necessarily as a replacement. The Committee considered that for the majority, lanthanum would be combined with calcium-phosphate binders. The Committee noted that there is no data relating to the benefit of the addition of these agents into regiments with currently funded phosphate lowering binders for the treatment of hyperphosphatemia in CKD.

8.23. The Committee noted the PHOSPHATE study, currently being undertaken in Australia and New Zealand, and noted that hard outcomes relating to any benefits for lowering phosphate in individuals with CKD may be clearer following publication of results from this study.

Suitability

8.24. The Committee noted that treatment with lanthanum carbonate or sevelamer carbonate would not replace current treatment for many individuals with hyperphosphataemia but would rather be in addition to their current treatment. The Committee considered that funding these treatments would add to already significant "pill burden" experienced by these individuals. However, the Committee considered that the impact of this is unclear and that if all medications were to be taken at the same time of day (ie three times daily with meals) adherence may not be impacted.

Cost and savings

8.25. The Committee considered that use of aluminium hydroxide in New Zealand would almost exclusively be for the treatment of hyperphosphataemia, and not use as antacid treatment. The Committee considered that individuals from this group are likely to access sevelamer or lanthanum as both medications can be utilised as an add-on to calcium or aluminium based binders or replacement therapy.

8.26. The Committee considered that the number of individuals with chronic renal failure potentially requiring treatment with lanthanum carbonate or sevelamer carbonate would be two to three times the number of individuals receiving dialysis.

8.27. The Committee considered that there would be a subset of patients currently receiving aluminium hydroxide who would switch over to lanthanum carbonate or sevelamer carbonate due to the potential toxicities associated with aluminium but considered that this number would be small.

Summary for assessment

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

Population	Adults with CKD with hyperphosphatemia, significant renal disease, currently taking a calcium-based binder or trialled a calcium-based binder who has not experienced phosphate reduction or intolerable toxicity. Finally, individuals have a calcium-phosphate product of at least 4.5 mmol/L[2.]
Intervention	**Lanthanum carbonate** Initially 750mg once daily, increasing as necessary every 2 to 3 weeks until acceptable serum phosphate levels are achieved and maintained (usually between 1500mg to 3000mg once daily). Median dose of between 750mg-1500mg, with the median dose changing according to the length of time patients are on treatment (Ogata et al. JAMA. 2021; 325: 1946-1954).
Comparator(s)	Calcium based binders, mostly calcium carbonate Small number or people on aluminium hydroxide may also switch to lanthanum carbonate
Outcome(s)	**Phosphate serum levels:** • Lanthanum carbonate is associated with reductions in serum phosphate levels comparable to calcium carbonate (Kasai et al. Ther Apher Dial. 2012; 16: 341-349) **All cause death** • Lanthanum carbonate displayed no significant difference in all-cause death when compared to calcium carbonate (HR= 1.10, 95% CI 0.88-1.37; p=0.42). Ogata et al. JAMA. 2021; 325: 1946-1954
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

9. Eculizumab for the treatment of atypical Haemolytic Uraemic Syndrome (aHUS) in adults and children

Application

9.1. The Advisory Committee reviewed the application for eculizumab in the treatment of atypical Haemolytic Uraemic Syndrome (aHUS)

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

Recommendation

9.3. The Advisory Committee **recommended** that eculizumab be listed with a **low** priority within the context of treatment of renal diseases subject to the following Special Authority criteria:

Initial application
Applications only from nephrologist or haematologist. Approvals valid for 12 weeks.
All of the following:

1. Patient has active and progressive thrombotic microangiopathy caused by atypical haemolytic uraemic syndrome; and
2. Patient has a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) (ADAMTS-13) activity of great than or equal to 10% on a blood sample taken prior to plasma exchange or infusion; and
3. Patient has had a confirmed negative result for Shiga toxin-producing *Escherichia coli* or other infections if they have had diarrhoea in the preceding 14 days

Renewal - Continuation of treatment

Applications only from a nephrologist or haematologist. Approvals valid for 12 weeks.

1. The treatment remains appropriate, and the patient is benefiting from the treatment

Renewal following relapse

Applications only from nephrologist or haematologist. Approvals valid for 12 weeks

1. The patient has experienced a satisfactory response to treatment previously
2. The treatment remains appropriate for the patient

9.4. In making this recommendation, the Committee considered:

9.4.1. The strong evidence of high health need due to the severity of symptoms and high mortality rates experienced by individuals with aHUS.

9.4.2. The unmet health need for individuals with aHUS as currently funded treatments are unable to target the underlying pathophysiological process causing symptomatic disease.

9.4.3. The high-quality evidence for the health benefit of eculizumab, with strong evidence that individuals with aHUS experience improved renal function, when treated with eculizumab.

9.4.4. The substantial cost of eculizumab treatment and the uncertainty over whether initiating discontinuation following disease remission is safe. The Committee noted that treatment for these individuals may be lifelong.

Māori impact

9.5. The Committee discussed the impact of funding eculizumab for the treatment of aHUS on Māori health areas of focus and Māori health outcomes. The Committee noted that aHUS is a rare disease and there is no information currently avaliable that demonstrates that Māori individuals are disproportionately impacted by aHUS.

Health need

9.6. The Committee noted that aHUS is characterised by progressive episodes of microangiopathic haemolytic anaemia, thrombocytopenia, and acute kidney injury. The Committee noted that 20% of individuals with aHUS can also experience extra-renal complications involving the central nervous, cardiovascular, pulmonary, gastrointestinal, and skeletal systems.

9.7. The Committee noted that the complement pathway forms part of the innate immune system, and that the pathway leads to the formation of the C5b-9 membrane attack complex, which inserts pores into the target cell membrane leading to osmotic lysis and cell death. The Committee noted that the alternative complement pathway is self-amplifying, with constant low levels of activation requiring continuous regulation.

9.8. The Committee noted that individuals with aHUS, can have inherited or sporadically acquired genetic mutations in the regulatory inhibitors of the complement system. The Committee noted that approximately 65% of individuals with aHUS result from genetic mutations in the complement regulatory genes... The Committee noted the genetic mutations that have been detected in individuals and are associated with aHUS including: CFH, CFI, C3, MCP, THBD, CFB, DAF, CFHR1/3, CD59, CR and anti-CFH antibodies. The Committee noted that sporadic manifestations of aHUS have resulted following pregnancy, gastro-intestinal or pulmonary (bacterial/ viral) infection, autoimmune conditions, organ transplants and drug treatments. The Committee noted that the underlying genetic mutation remains unidentified in approximately 30% of individuals with aHUS.

9.9. The Committee noted that aHUS is a rare and life-threatening disease. The Committee noted that clinical presentation of aHUS is heterogenous, and the symptoms of aHUS can arise progressively over time, or suddenly, with these

individuals being critically ill and requiring immediate medical attention. The Committee noted that aHUS can occur at any age and irrespective of the mutation type, approximately 67% of individuals with aHUS are affected during childhood. The Committee noted that aHUS is difficult to diagnose, and normally occurred as a process of elimination of other indications.

9.10. The Committee noted that mutation type has prognostic implications. The Committee noted that there is a 50% likelihood overall that an individual will experience end-stage renal disease, a 30% likelihood that the individual will experience neurologic symptoms and 25% likelihood that the individual will die during the acute phase of aHUS. The Committee noted that individuals with CFH, CFB, C3, CFI, and anti-CFH antibodies mutations being associated with the highest risk of end-stage renal disease and or death at the first presentation of the disease or within one year of symptom presentation. Particular mutations such as CFH, CFB and C3 have the highest risk of progression to end stage kidney disease and recurrence following kidney transplantation. The Committee noted that individuals with the MCP mutation are likely to have a better prognosis as the effect on renal outcomes can be milder, however recurrent episodes of MCP-mediated aHUS are more frequent in comparison to other aHUS-associated genetic mutations (about 10-15% of individuals with aHUS).

9.11. The Committee noted there is an estimated prevalence of 2.40 per million adults with aHUS in Australia (Mallett et al. Orphanet J Rare Dis. 2014; 9: 98). The Committee noted an epidemiology systematic literature review (Yan et al. Clin Epidemiol. 2020; 12: 295-305) which indicated that the global incidence rate for aHUS in individuals under the age of twenty years old to range between 0.23 and 0.75 per million annually and the global incidence rate for aHUS in all-ages was between 0.23 to 1.9 per million population. According to patient data from clinicians at Starship hospital, the Committee considered that the incidence for paediatric individuals (15 and younger) was 1.2 per million for New Zealand. The Committee noted that aHUS individuals make up about 0.2% of the Australian chronic kidney disease cohort (Mallett et al. Orphanet J Rare Dis. 2014; 9: 98).

9.12. The Committee noted that there was no evidence that aHUS disproportionally affected Māori, Pacific people or other groups already experiencing health inequities in the New Zealand population, which the Committee considered was likely due to the rarity of aHUS.

9.13. The Committee noted that there is an unmet health need for individuals with aHUS as there are currently no treatment protocols or funded therapies available that address the underlying pathophysiologic process of aHUS and individuals are limited to supportive therapies to manage the symptoms of aHUS.

9.14. The Committee noted that supportive treatments available include plasma therapy (plasma exchange or plasma infusion, corticosteroids, immunosuppressive therapies, renal transplantation, or dialysis. The Committee noted that due to the heterogeneity of the disease the response to therapeutic regimens also differs and must be personalised for the individual. The Committee noted that plasma exchange removes the genetically defective complement proteins or associated antibodies and replaces them with normal functioning proteins. The Committee noted that the response to plasma therapy varies between individuals and some patients will develop resistance to plasma exchange or infusions over the course of their experience of the disease. Plasma exchange also requires dedicated vascular access which over time will become depleted due to complications of line sepsis and vascular stenosis and thrombosis.

9.15. The Committee noted that when the disease is active and unmanaged, the individuals become progressively more ill and the risk of permanent kidney damage becomes

high, leading to a requirement for renal replacement therapies, which require a number of hospital stays which negatively impacts the individual's and whānau quality of life. The Committee noted that combined liver-kidney transplant is another treatment option for advanced disease but is associated with considerable morbidity and mortality and internationally eculizumab is the preferred treatment for individuals with aHUS.

9.16. The Committee noted there is a severe unmet health need for individuals with aHUS due to the lack of available therapies. The Committee noted that given the characteristics of aHUS (rarity, chronicity, and childhood onset of aHUS) providing therapeutic options to improve the quality of life for individuals with aHUS is a government health priority.

Health benefit

9.17. The Committee noted that eculizumab is a humanised monoclonal antibody that binds with high affinity to complement thereby preventing the formation of the membrane attack complex through the alternative pathway.

9.18. The Committee noted that eculizumab treatment can increase the likelihood of the individual contracting meningococcal disease.

9.19. The Committee noted the following study which included two phase 2 prospective single-arm trials (Lengendre et al. N Engl J Med. 2013; 368: 2169-81) as the primary evidence for the efficacy of eculizumab in the treatment of individuals with aHUS:

9.19.1. The first trial involved 17 individuals with aHUS and 12 years or older, weighing at least 40kg with abnormal or low platelet count and renal damage. Eculizumab was administered intravenously at a dose of 900 mg per week for 4 weeks, a dose of 1200 mg 1 week later, and a maintenance dose of 1200 mg every 2 weeks for 26 weeks, with a continuation of the trial to 62-64 weeks. Fifty-three percent of the participants with an abnormal platelet count at baseline had a normal platelet count (≥150×109/L) by day 7, and 87% had platelet counts that remained normal at both weeks 26 and 64. Normalisation of platelet count and lactate dehydrogenase levels occur in 88% of participants. 15 of the 17 participants (88%) had thrombotic microangiopathy event–free status through to week 26.13 individuals extended treatment to 64 weeks and 100% had thrombotic microangiopathy event–free status. The mean increase in eGFR from baseline after 26 weeks of treatment was 32 ml/ minute /1.73 m^2 (95% CI, 14 to 49; P = 0.001). Dialysis was discontinued in four of five participants (80%) who had required dialysis at the time of initiation of eculizumab, and these participants remained dialysis-free throughout eculizumab treatment. Whilst receiving eculizumab 88% of individuals no longer required plasma exchange or infusion.

9.19.2. The second trial involved 20 individuals who were 12 years or older, weighing at least 40kg with renal damage and no variation greater than 25% in platelet count. Eculizumab was administered intravenously at a dose of 900 mg per week for 4 weeks, a dose of 1200 mg 1 week later, and a maintenance dose of 1200 mg every 2 weeks for 26 weeks, with a continuation of the trial to 62-64 weeks. 16 of 20 participants (80%) experienced complete inhibition of complement-mediated thrombotic microangiopathy indicated by thrombotic microangiopathy event-free status for at least 12 weeks (no decrease in platelet count of >25%, no plasma therapy, no initiation of dialysis)) by week 26; this proportion increased to 85% through the median treatment duration of 62 weeks. Four participants did not meet the end point at 26 weeks because of a transient decrease in the platelet count of more than 25% from baseline, although all four maintained normal platelet counts. The mean increase in eGFR from baseline

after 26 weeks of treatment was 6 ml/ minute /1.73 m^2 (95% CI, 3 to 9; P<0.001). With initiation of eculizumab, plasma exchange or infusion was discontinued in all participants, and no new dialysis was required. Normalisation of platelet count and lactate dehydrogenase levels occur in 90% of participants. With initiation of eculizumab, plasma exchange or infusion was discontinued in all individuals, and no new dialysis was required.

9.20. The Committee noted the following trials relating to the efficacy of eculizumab for the treatment of aHUS:

9.20.1. Greenbaum et al Kidney Int. 2016; 89: 701-11

9.20.2. Fakhouri et al. Am J Kidney Dis. 2016; 68: 84-93

9.20.3. Menne et al. Clin Kidney J. 2018; 12:196-205

9.21. The Committee noted that aHUS is a rare disease and considered that the strength and quality of the evidence for benefit of treatment with eculizumab was good. The Committee noted that eculizumab can provide the individual with a high likelihood that they would experience improved renal function and significantly reduce the risk of developing end-stage renal disease, thus avoiding dialysis, renal or liver transplant, and pre-mature death.

9.22. The Committee noted that New Zealand's incidence rates are similar to the global incidence rates and that individuals with aHUS in New Zealand are likely to experience significant health benefit if eculizumab were to be funded.

9.23. The Committee noted that some individuals can experience complete remission of the symptoms of aHUS following eculizumab therapy and these individuals may be able to discontinue eculizumab therapy. However, the Committee considered that the evidence for discontinuing eculizumab to be uncertain and in clinical practice treatment will likely be lifelong, however noted that research into safely discontinuing eculizumab is ongoing. The Committee noted the following observational studies regarding the discontinuation, re-initiation, and long-term efficacy of eculizumab:

9.23.1. Menne et al. BMC Nephrol. 2019; 20: 125:93 individuals (0–80 years of age) treated with eculizumab, 51 (55%) remained on eculizumab and 42 (45%) discontinued; for those who discontinued, 21 (50%) reinitiated therapy over the 6-years of trial participation. individuals who reinitiated eculizumab had similar baseline clinical characteristics to individuals who remained on eculizumab, with higher likelihood of genetic/autoimmune complement abnormalities, more prior thrombotic microangiopathy, and longer disease course versus those who did not reinitiate. Off-treatment thrombotic microangiopathy manifestation rates were higher in those aged < 18 years at diagnosis, with identified genetic/autoimmune complement abnormalities, or history of multiple thrombotic microangiopathies prior to eculizumab initiation.

9.23.2. Fakhouri et al. Blood. 2021; 137: 2438-2449: Fifty-five individuals (including 19 children) discontinued eculizumab following a mean treatment duration of 16.5 months. Twenty-eight individuals (51%) had rare variants in complement genes, mostly in *MCP* (n=12; 22%), *CFH* (n=6; 11%), and *CFI* (n=6; 10%). At eculizumab discontinuation, 17 (30%) and 4 individuals (7%) had stage 3 and 4 chronic kidney disease, respectively. During follow-up, 13 individuals (23%; 6 children and 7 adults) experienced aHUS relapse. In multivariable analysis, female sex, and presence of a rare variant in a complement gene were associated with an increased risk of aHUS relapse, the requirement for dialysis during a previous episode of acute aHUS was not. Of the 13 relapsing individuals, all of whom restarted eculizumab, 11 regained their baseline renal

function and 2 had a worsening of their pre-existing chronic kidney disease, including 1 patient who progressed to end-stage renal disease.

9.23.3. Bouwmeester et al. Kidney Int Rep. 2022; 8 :91-102: 21 Individuals received a median of 13.6 weeks (range 2.1-43.9) of eculizumab therapy and were monitored for 4 years. In 17 individuals (81%), a complement genetic variant or antibodies against factor H were identified. All individuals showed full recovery of haematological thrombotic microangiopathy parameters after the start of eculizumab. Relapse occurred in a median of 19.5 weeks (range 14.3 – 53.6) in 4 individuals. Re-initiation of treatment with eculizumab resulted in full recovery of kidney function and recovery of haematological thrombotic microangiopathy parameters. Of all individuals with ≥1 year of follow-up after eculizumab discontinuation (12 of 18), the relapse rate was 33%.

9.24. The Committee noted that response to eculizumab can vary between individuals and following eculizumab infusions some individuals experiencing remission may be able to discontinue therapy, and experience durations without symptoms of aHUS. The Committee noted that these individuals may require periodic eculizumab therapy if they experience an aHUS trigger-event such as an infection, resulting in remission failure. The Committee noted that some individuals with aHUS may experience immediate relapse of symptoms following discontinuation of eculizumab and may require life-long therapy to manage the aHUS associated symptoms.

9.25. The Committee noted that discontinuation of eculizumab is reported to be safe in most individuals with aHUS, and there is increasing liklihood between 25 – 50 % of relapse depending on the gene which is mediating the disease (Brodsky R. Blood. 2021; 137: 2419-2420).

Suitability

9.26. The Committee noted that eculizumab must be administered intravenously in hospital or in an appropriate infusion setting and some people may have difficulty accessing these services, such as those living rurally.

9.27. The Committee noted that individuals who receive eculizumab require vaccination to protect against meningococcal infection (Neisseria meningitidis) at least 2 weeks prior to receiving eculizumab unless the risk of delaying therapy outweighs the risk of meningococcal infection. The Committee noted that individuals should be revaccinated according to current national vaccination guidelines against serogroups A, B, C, Y and W135. The Committee noted that individuals who are unable to be vaccinated 2 weeks prior must receive treatment with prophylactic antibiotics until 2 weeks after vaccination.

Cost and savings

9.28. The Committee noted that the population that would be treated would be all individuals with aHUS and there are approximately 20 individuals living with aHUS in New Zealand currently.

9.29. The Committee considered that eculizumab treatment would be ongoing.

9.30. The Committee noted there was no clear treatment protocol for aHUS in NZ, as each individual is likely to require different treatment, therefore the frequency and duration of plasma therapy in the comparator is unclear.

9.31. The Committee considered that individuals may still have plasma therapy whilst on eculizumab treatment, however noted the results of the Lengendre et al study, where most individuals were able to cease plasma therapy while under treatment with eculizumab.

Summary for assessment

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

Population	People with diagnosed aHUS, with active progressive thrombotic microangiopathy
Intervention	*Eculizumab* *Adults* Adults (≥ 18 years of age) and children (<18 years ag age and ≥ 40kg) 900 mg of eculizumab via a 25 - 45-minute intravenous infusion every week for the first four weeks. Followed with a maintenance dose of 1200 mg via a 25–45-minute infusion in the fifth week and every two weeks thereafter. Children (< 40kg) Weight determined dosage. 30 to <40 kg: 600 mg on weeks 1 and 2, 900 mg on week 3; then 900 mg every 2 weeks 20 to <30 kg 600 mg on weeks 1 and 2 600 mg at week 3; then 600 mg every 2 weeks 10 to <20 kg 600 mg on week 1 300 mg on week 2; then 300 mg every 2 weeks 5 to <10 kg 300 mg on week 1 300 mg on week 2; then 300 mg every 3 weeks Meningococcal vaccination ACWY & B (2 weeks prior to eculizumab) for all (Plus, antibiotic cover as required) Individuals may have concurrent plasma therapy, and/or renal transplant. Treatment ongoing until disease recurrence. On recurrence, treatment is best supportive treatment.
Comparator(s) (NZ context)	Best supportive treatment: • Plasma exchange/plasma infusion • Dialysis (late disease stage) • Renal or renal/hepatic transplant (late disease stage)
Outcome(s)	• TMA event free status • Prevention or delay of ESRD • Reduced need for dialysis • Reduced kidney transplantation • Improved health related quality of life (HRQOL) • Mortality
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the target population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).	

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

TMA - thrombotic microangiopathy, ESRD – end stage renal disease, aHUS – atypical haemolytic uremic syndrome.

10. Rituximab for the treatment of Class III and IV active lupus nephritis as part of the induction phase of therapy

Application

10.1. The Advisory Committee reviewed the application for [application] in the treatment of Lupus Nephritis class III or IV for induction therapy

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

Recommendation

10.3. The Advisory Committee **recommended** that widening access for rituximab to include induction phase therapy to manage active lupus nephritis class III and IV be **declined**.

10.4. In making this recommendation, the Committee noted that inadequately managed lupus nephritis class III and IV can increase the risk of progression of the disease and end-stage kidney disease. The Committee noted the unmet health need due to individuals being unable to be appropriately managed on the current available therapies. The Committee noted that there was no evidence that individuals would experience improved health outcomes if they received rituximab as part of the induction therapy and rituximab would not address the unmet health need of these individuals.

Discussion

Māori impact

10.5. The Advisory Committee discussed the impact of funding rituximab for the induction phase for the treatment of active lupus nephritis class III or IV on Māori health areas of focus and Māori health outcomes. The Committee noted that Māori are disproportionally affected by lupus nephritis class III and IV; Māori are less likely to be appropriately managed on current therapeutic regimens due to practical healthcare barriers, and Māori experience higher rates of end stage renal disease and mortality compared to non-Māori, non-Pacific people (Concannon et al. Lupus. 2022; 31: 1671-1678).

Health need

10.6. The Committee noted that lupus nephritis is a severe complication of systemic lupus erythematosus which occurs when the immune system inadvertently attacks the kidneys, leading to inflammation and organ damage if not adequately managed. The Committee noted that lupus nephritis can harm the ability of the kidneys to properly remove waste from blood, control the body's fluid status, regulate hormone production, and salt availability required for managing blood pressure and blood volume.

10.7. The Committee noted that renal involvement occurs in up to 50% of individuals with systemic lupus erythematosus during the disease course and has been estimated to lead to end-stage kidney disease in about 10% of individuals. The Committee noted there are several classes of lupus nephritis which are identified on renal biopsy.

10.8. The Committee noted that current steroid and immunosuppressant therapies can have intolerable side effects negatively impacting an individual's general health, mental wellbeing and fertility and these adverse effects could lead to discontinuation of the treatment.

10.9. The Committee noted that progressive and unmanaged lupus nephritis increases the risk of end-stage renal disease and the individual requiring renal replacement therapies such as dialysis and renal transplantation. The Committee noted lupus nephritis is associated with severe comorbidities such as infections, cardiovascular complications, and increased risk of malignancy.

10.10. The Committee noted that progression of lupus nephritis, end stage kidney disease and experiencing comorbidities relating to their condition can impact an individual's ability to perform daily tasks, affect the individual's quality of life and survival and renal replacement therapies pose significant cost to the healthcare system.

10.10.1. The Committee noted that the number of individuals with lupus nephritis class III and IV in New Zealand was unknown. The study by Concannon et al (2022) estimated that there may be 10-25 new individuals per year diagnosed with lupus nephritis class III or IV in New Zealand who may require treatment. The Committee noted that not all individuals with lupus nephritis had a renal biopsy unless class III or IV was suspected.

10.10.2. The Committee noted an observational study of children diagnosed with biopsy proven lupus nephritis seen by Kidz First paediatric rheumatology and/or Starship renal services between 1992 and January 2018 (Concannon et al. Lupus. 2022; 31: 1671-1678). The Committee noted that in this study there were 42 individuals diagnosed with childhood onset lupus nephritis, 67% were Māori or Pacific people and there was an estimated annual incidence rate of 0.01 per 100,000 people. The Committee noted that, on average, childhood onset lupus nephritis was diagnosed at age 11.9 years.

10.10.3. The Committee noted that Concannon et al (2022) found that Māori and Pacific people are disproportionally affected by lupus nephritis class III and IV, and they are also less likely to be appropriately managed on current therapeutic regimens due to practical healthcare barriers, institutional racism, discrimination and devaluation of spiritual and cultural practices and experience higher rates of end stage kidney disease and mortality in comparison to non-Māori, non-Pacific people (Concannon et al. Lupus. 2022; 31: 1671-1678).

10.11. The Committee noted the current Kidney Disease: Improving Global Outcomes: guidelines (KDIGO) for the management of active lupus nephritis class III and IV:

10.11.1. Individuals with active lupus nephritis class III or IV without membranous component should be treated initially with glucocorticoids and either low dose cyclophosphamide or mycophenolic acid analogues.

10.11.2. A regimen of reduced-dose glucocorticoids following a short course of methylprednisolone pulses may be considered during the initial treatment of active lupus nephritis when both the kidney and extra-renal disease manifestations show satisfactory improvement.

10.11.3. Intravenous cyclophosphamide should be used as the initial therapy for active Class III and Class IV lupus nephritis in patients who may have difficulty adhering to an oral regimen.

10.11.4. A mycophenolic acid analogues-based regimen is the preferred initial therapy of proliferative lupus nephritis for patients at high risk of infertility, patients who have a moderate to high prior cyclophosphamide exposure.

10.11.5. Triple therapy with glucocorticoids, low dose mycophenolic acid analogues and a calcineurin inhibitor (cyclosporine or tacrolimus) should be reserved for patients who cannot tolerate full dose mycophenolic analogues or cyclophosphamide regimes.

10.11.6. In individuals with eGFR of at least 45mL/min per 1.73m3 voclosporin can be added to the mycophenolic acid analogues and glucocorticoids regimen as initial therapy for 1-year.

10.11.7. There is an emerging role for B-lymphocyte targeting biologics in the treatment of lupus nephritis class III and IV and Belimumab can be added to standard therapy.

10.11.8. Rituximab may be considered for patients with persistent disease activity or repeat flares.

10.11.9. Other therapies, such as azathioprine or leflunomide combined with glucocorticoids, may be considered in lieu of the recommended initial drugs for proliferative lupus nephritis in situations of patient intolerance, lack of availability, and/or excessive cost of standard drugs, but these alternatives may be associated with inferior efficacy, including increased rate of disease flares and/or increased incidence of drug toxicities.

10.12. The Committee noted the current special authority for Rituximab for the treatment refractory systemic lupus erythematosus. The Committee noted that rituximab is available for individuals with relapsed/refractory systemic lupus erythematosus with an immediate and severe threat of death or organ failure which includes severe lupus nephritis. The Committee considered that determining whether the disease is refractory to standardised treatments can be difficult and noted that there are no factors that can reliably predict and identify a subgroup of patients likely to be inadequately managed with standardised treatment.

Health benefit

10.13. The Committee noted evidence from two relevant randomised controlled studies, the EXPLORER study (Merrill et al. Arthritis Rheum. 2010; 62: 222–233) and the LUNAR study (Rovin et al. Arthritis Rheum. 2012; 64:1215-26).

10.13.1. The EXPLORER trial, which involved 257 patients who had moderate to severe active systemic lupus erythematosus assessed by the British Isles Lupus Assessment scale (BILAG). Patients were randomised 2:1 to receive 1000mg rituximab or placebo on days 1, 15, 168, and 182 in addition to prednisone (0.5-1mg/kg tapered to 10mg over 10 weeks) and background immunosuppressant therapy. The study reported no significant differences between rituximab and placebo on primary and secondary endpoints in the study.

10.13.2. The LUNAR study was a randomised controlled study in 144 patients with class III or class IV lupus nephritis treated concomitantly with mycophenolate and corticosteroids. Patients were randomized 1:1 to receive rituximab (1000 mg) or placebo on days 1, 15, 168, and 182 both in combination with prednisone 0.75 mg/kg tapered to 10 mg over 10 weeks. The primary endpoint measured the renal response status, irrespective of individuals experiencing flares of symptoms following 52 weeks of the therapeutic regimen. Overall, there was no significant differences in the complete or partial renal response status between rituximab and placebo groups.

10.14. The Committee considered that the strength and quality of the evidence for the use of rituximab in the induction phase of therapy for lupus nephritis class III or IV to be weak. The Committee noted that rituximab demonstrated no efficacious benefit when used as an add on to standard level of care when treating individuals with lupus

nephritis. The Committee noted rituximab is not recommended in the current KDIGO guidelines in the induction phase of treating class III-IV lupus nephritis.

Suitability

10.15. The Committee noted that rituximab is an infusion-based therapy and would require nursing and infusion resource. The Committee noted that not all individuals would have access to an appropriate infusion setting.

Cost and Savings

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

Population	People with class III and IV lupus nephritis, requiring initial therapy to induce resolution of inflammatory and immunologic activity
Intervention	Rituximab, in combination with high-dose corticosteroids and either cyclophosphamide or mycophenolate mofetil: • Rituximab administered as 1000mg infusions (on days 1, 14, 168 and 182) • Followed by maintenance therapy with low dose prednisone, azathioprine, or mycophenolate, along with hydroxychloroquine and cotrimoxazole.
Comparator(s) (NZ context)	High-dose corticosteroids, in combination with cyclophosphamide or mycophenolate mofetil • Followed by maintenance therapy with low dose prednisone, azathioprine, or mycophenolate, along with hydroxychloroquine and cotrimoxazole.
Outcome(s)	No significant benefit with rituximab vs currently funded induction treatment

Table definitions:

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

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

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

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