Nephrology Subcommittee of PTAC
Meeting held 2 December 2014

(minutes for web publishing)

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

The Nephrology Subcommittee may:

1. recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
2. 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
3. recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

These Subcommittee minutes were reviewed by PTAC at its meeting on 7 & 8 May 2015, a record of which is now available.

1 Matters arising and correspondence

Calcium acetate

1.1 The Subcommittee noted that PHARMAC had received an application from the Paediatric Renal Service at Starship Children's Health for the funding of a suitable alternative phosphate binder following the discontinuation of the Titralac brand of calcium carbonate tablets.

1.2 The Subcommittee noted that PHARMAC sourced an alternative product for young children, listing calcium carbonate oral liquid on the Pharmaceutical Schedule in December 2012 but subsequently received clinical feedback that the product did not resolve all of the issues for this patient group. The Subcommittee noted that calcium carbonate oral liquid is effective in an acidic pH environment but not a neutral pH one which makes it an inappropriate treatment in patients also taking omeprazole. The Subcommittee also noted that administration of an oral liquid is problematic in school going children.

1.3 The Subcommittee noted that calcium acetate capsules (PhosLo) is potentially a useful treatment alternative as it works in a neutral pH environment and it is also more effective than calcium carbonate. It noted that calcium acetate capsules would meet the clinical need of both infant and adult populations. The Subcommittee also noted that when the contents of capsules are dissolved, there are fewer issues with precipitation when compared to the calcium carbonate oral liquid.

1.4 The Subcommittee noted that calcium acetate capsules are not currently registered in New Zealand. The Subcommittee **recommended** that calcium acetate capsules are funded as a phosphate binder with a medium priority. Drs Tonya Kara and William Wong refrained from voting on this funding application to manage potential conflict of interests.

2 Rituximab in nephrotic syndrome

Application

2.1 The Subcommittee noted that PHARMAC received a clinician application requesting for the current hospital restrictions for rituximab to be widened to include patients with idiopathic nephrotic syndrome (INS).

Recommendation

2.2 The Subcommittee **recommended** that access to rituximab in Section H of the Pharmaceutical Schedule is widened to include nephrotic syndrome with high priority subject to the following restriction criteria:

Initiation – nephrotic syndrome
Nephrologist
Limited to 4 weeks' treatment
All of the following:

1. Patient has nephrotic syndrome secondary to biopsy-proven minimal change disease or focal segmental glomerulosclerosis; and
2. Treatment with steroids and calcineurin inhibitors for at least a period of 3 months have been ineffective; and
3. The total rituximab dose used would not exceed the equivalent of 375 mg/ m^2 of body surface area per week for a total of 4 weeks.

Continuation - nephrotic syndrome
Nephrologist
Limited to 4 weeks' treatment
All of the following:

1. Patient was previously treatment with rituximab for nephrotic syndrome secondary to biopsy-proven minimal change disease or focal segmental glomerulosclerosis; and
2. Treatment with rituximab was previously successful but the condition has relapsed and the patient now requires repeat treatment; and
3. The total rituximab dose used would not exceed the equivalent of 375 mg/ m^2 of body surface area per week for a total of 4 weeks.

2.3 The Subcommittee deferred making a recommendation for the funding of rituximab in nephrotic syndrome secondary to membranous nephropathy until after the MENTOR study results are known. The Subcommittee considered that it would be appropriate for PHARMAC to continue to consider funding for rituximab in this setting on a case-by-case basis through the NPPA pathway.

2.4 The Decision Criteria particularly relevant to this recommendation are *(i) The health needs of all eligible people within New Zealand (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

2.5 The Subcommittee noted that the initial reports of use of rituximab for nephrotic syndrome in paediatric patients were released in 2004. Since then, there have been multiple reports for the use of rituximab in frequently relapsing (FRNS) and steroid dependant nephrotic syndrome (SDNS) in children. The Subcommittee noted that high success rates have been reported in these settings (Iijima et al. Lancet 2014; 384: 1273–81). The Subcommittee however noted that reported relapse rates have been variable but are likely to be high as well. The Subcommittee noted that the success rates of rituximab in steroid resistant nephrotic syndrome (SRNS) were lower.

2.6 The Subcommittee noted that most other studies of nephrotic syndrome are retrospective studies and the underlying disease pathology can be divided into

two main categories: (1) minimal change disease (MCD) / focal segmental glomerulosclerosis (FSGS) and (2) membranous nephropathy. The Subcommittee noted that in patients with MCD/ FSGS, the relapse free period with rituximab in longer in those with SDNS and FRNS as noted above. Rituximab would allow reduction or cessation of steroid and calcineurin inhibitors in these patients although almost all patients will relapse.

2.7 The Subcommittee noted the results from the Iijima et al study (Lancet 2014; 384:1273–81) which was a multicentre, double-blind, randomised, placebo-controlled study investigating the efficacy and safety in patients with FRNS and SDNS. This study involved mainly patients with MCD and FSGS. Treatment failure was reported in 10 patients in the rituximab group (42%) and 20 in the placebo group (83%). The Subcommittee noted that by the end of 1 year of follow-up, 17 patients in the rituximab group and 23 in the placebo group had relapsed; however, the median relapse-free period was significantly longer in the rituximab group (267 days, 95% CI 223–374) than in the placebo group (101 days, 70–155; HR 0·27, 95% CI 0·14–0·53; p<0·0001). The Subcommittee noted that all patients in the trial had relapsed after 19 months. The Subcommittee also noted that the daily dose of steroid use was significantly lowered with rituximab treatment (19.1 mg versus 8.37 mg, p<0.0001) but not in the placebo arm (18.02 mg versus 21.02 mg, p= 0.21). The Subcommittee noted that the mean period of B-cell depletion with rituximab was 148 days and levels returned to normal in all patients treated with rituximab by day 253.

2.8 The Subcommittee noted that an adjunct to the diagnosis of primary membranous nephropathy is to measure anti phospholipase A_2 receptor antibody titres but this test is not available in New Zealand. There is currently no published randomised controlled trial for rituximab in this pathology but a Phase 3 trial comparing ciclosporin and rituximab is in progress - the Membranous Nephropathy Trial of Rituximab (MENTOR)(trial identifier: NCT01180036). The Subcommittee considered that published studies of rituximab in membranous nephropathy have reported complete response rates of about 10-30% and partial response rates as high as 50% (Busch et al. Clinical Nephrology 2013; 80(2): 105-113 and Ruggenenti et al. J Am Soc Nephrol 2012; 23: 1416-1425).

2.9 The Subcommittee considered that there were few increased side effects from rituximab therapy in nephrotic syndrome. The Subcommittee noted that there have been rare reports of multifocal leukoencephalopathy associated with rituximab treatment. Infusion reactions and infections are increased with rituximab treatment as well as lung disease such as rapidly progressive lung fibrosis. This is a rare complication but is associated with a high mortality rate.

2.10 The Subcommittee noted that there is a high clinical need for an effective treatment in nephrotic syndrome. It noted also that the incidence of nephrotic syndrome is higher in Maori and Pacific peoples. The Subcommittee noted that current funded treatments for nephrotic syndrome include ciclosporin, prednisone or prednisolone. Members noted that PHARMAC has assessed and ranked a funding application for tacrolimus for this indication. The Ponticelli regimen (cyclophosphamide, high dose steroids and chlorambucil) is currently used in the treatment of membranous nephropathy. The Subcommittee noted that in the nephrology setting, rituximab would be given as 375mg/m^2 weekly dose for up to

4 cycles. The Subcommittee noted that instead of replacing current treatments, rituximab could be used in conjunction with them but the dose of calcineurin inhibitor and steroid use could be reduced. The Subcommittee noted that long-term calcineurin inhibitor and steroid use is associated with toxic side-effects.

2.11 The Subcommittee noted that rituximab is more effective in FRNS and SDNS when compared to SRNS but it considered that there is no alternative treatment in SRNS. The Subcommittee also considered that there is currently a better level of evidence of rituximab in patients with MCD and FSGS when compared to membranous nephropathy. The Subcommittee considered that it would be appropriate to await the results of the MENTOR trial before it made a recommendation for funding of rituximab in membranous nephropathy. The Subcommittee noted that if rituximab was funded with the recommended criteria above, it would be accessed each year by approximately 5 paediatric patients for SRNS, 5 paediatric patients for SDNS and 10 adults.

3 Sevelamer hydrochloride in hyperphosphataemia

Application

3.1 The Subcommittee noted that PHARMAC received a funding application from Sanofi for sevelamer hydrochloride for the treatment of hyperphosphataemia associated with chronic kidney disease.

Recommendation

3.2 The Subcommittee **recommended** that the funding application for sevelamer hydrochloride for the treatment of hyperphosphataemia associated with chronic kidney disease is declined.

3.3 The Subcommittee **recommended** that PHARMAC seek a funding application for sevelamer carbonate once it is Medsafe-registered.

3.4 The Decision Criteria particularly relevant to this recommendation are *(i) The health needs of all eligible people within New Zealand (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

3.5 The Subcommittee noted that the funding application for the funding of sevelamer hydrochloride was reviewed by PTAC at its meeting in February 2013. The Subcommittee noted that PTAC recommended the application be declined because it considered that the evidence for sevelamer hydrochloride was of poor

quality and of mixed strength. PTAC also considered that aluminium-based binders, which were not considered by the applicant, were a relevant comparator. It considered that there were also safety issues with sevelamer hydrochloride, and requested that an application for the carbonate formulation be sought instead.

3.6 The Subcommittee noted that Sanofi provided an update to their submission which was reviewed by PTAC at its November 2013 meeting and again PTAC's recommendation was for the application to be declined. Shortly after, the Subcommittee noted that PHARMAC received a second resubmission for sevelamer hydrochloride in response to the November 2013 PTAC minutes. This resubmission as well as previous submissions has now been referred to this Subcommittee for review, after which it would be forwarded to PTAC for review. Sanofi has provided some additional information in this resubmission and have requested an alternative proposed Special Authority criteria be considered that would help focus treatment to patients on dialysis with hyperphosphataemia whose serum calcium x phosphate product is >4.0mmol/L and in whom other treatments have failed.

3.7 The Subcommittee noted the results of the DCOR study (Suki WN et al. Kidney International 2007;72:1130–37) where the all-cause mortality rate in the sevelamer hydrochloride arm was 15.0 per 100 patient-years and the calcium arm mortality rate was 16.1 per 100 patient-years (HR 0.93, 95% CI 0.79–1.10; P = 0.40). The Subcommittee noted that this result was not statistically significant. The Subcommittee also noted that this was also the case when looking at the cardiovascular specific mortality rate. The Subcommittee noted that there was a high drop out rate but for those patients remaining on study for at least 2 years (43% of the population), the Subcommittee noted that a difference between groups favouring sevelamer, appears to emerge (time–treatment interaction P = 0.02).

3.8 The Subcommittee noted that in subjects over65 years of age (44% of the study population), the all-cause mortality rate was 18.2 per 100 patient-years for the sevelamer group and 23.4 per 100 patient-years for the calcium group (hazard ratio = 0.77, 95% CI: 0.61–0.96, P= 0.02). The Subcommittee also noted that in this age group, the mean number of hospitalisations per year and lengths of stay were numerically lower in the sevelamer arm.

3.9 The Subcommittee noted the results of the RIND study of sevelamer in patients new to dialysis (Block GA et al. Kidney International 2007;71:438–41). The mortality rate was higher in subjects treated with calcium binders (10.6/100 patient years, CI 6.3–14.9) when compared to those randomized to sevelamer (5.3/100 patient years, CI 2.2–8.5, P=0.05). The Subcommittee noted that coronary artery calcification was a significant predictor of mortality in patients (P= 0.002).

3.10 The Subcommittee noted the results of the Jamal et al meta-analysis (Lancet. 2013 ;382(9900):1268-77) which reviewed the effect of calcium-based and non-calcium-based (sevelamer and lanthanum) phosphate binders on mortality in chronic kidney disease. The study reported a 22% reduction in all-cause mortality in patients treated with non-calcium-based phosphate binders (RR 0.78, 95% CI

0.61-0.98). In patients on dialysis, mortality was reduced by 12% (RR 0.88, 95% CI 0.79-0.99).

3.11 The Subcommittee reviewed the results of the Di lorio et al study (Clin J Am Soc Nephrol 2012;7:487–93) which was published after the Jamal et al meta-analysis and was an open-label RCT comparing sevelamer and calcium carbonate in pre-dialysis patients. The Subcommittee noted that the rate of all-cause mortality, dialysis inception, and the composite end point was significantly less frequent (log-rank test = 11.46; P<0.01) among patients randomized to sevelamer. The Subcommittee also noted that the final cumulative percentage of de novo onset of coronary artery calcification (CAC) was 12.8% in sevelamer-treated patients and 81.8% in calcium carbonate–treated patients; in the latter group, the increase in CAC score was also greater. The Subcommittee noted that episodes of hypercalcemia were more frequent in patients taking calcium carbonate than in those taking sevelamer (n=82 (78%) versus n=6 (5%); P<0.01). The Subcommittee however considered that the patient group which is the subject of this funding application is different to the patient group in this study.

3.12 The Subcommittee noted that sevelamer hydrochloride has been associated with gastrointestinal side effects and worsening of metabolic acidosis. This would impact on its tolerability with patients. The Subcommittee considered that overall, the evidence for sevelamer hydrochloride was of low quality and weak strength. The Subcommittee noted that the results of the DCOR study was not statistically significant, the results of the Jamal et al meta-analysis did not differentiate sevelamer and lanthanum whilst the Di lorio et al study was not specific to the patient group proposed in the funding application.

3.13 The Subcommittee noted that PTAC had identified aluminium-based binders as a potential treatment alternative. The Subcommittee noted that in line with the KDIGO (Kidney Disease Improving Global Outcomes) guidelines, long-term aluminium-containing phosphate binders should be avoided in patients with chronic kidney disease stages 3-5D (D indicates dialysis).

3.14 The Subcommittee noted the high cost of sevelamer hydrochloride and considered that its funding would be difficult to justify given the poor level of evidence. The Subcommittee noted that there are currently 2500 patients in New Zealand on dialysis and about 2500 patients who are pre-dialysis. The Subcommittee noted that it would be difficult to define restriction criteria to target treatment to patients most likely to benefit. The Subcommittee noted that the funding of the product would be associated with significant fiscal risk with a high uptake but only a small proportion of those patients would obtain significant benefit.

3.15 The Subcommittee noted that a new formulation of sevelamer is currently being reviewed by Medsafe for registration – sevelamer carbonate. The Subcommittee noted that the carbonate formulation of sevelamer could have a better safety profile and a funding application for that formulation should be sought.

4 Cinacalcet in hyperparathyroidism

Application

The Subcommittee noted a memorandum from PHARMAC staff regarding cinacalcet for the treatment of hyperparathyroidism.

Recommendation

4.1 The Subcommittee **recommended** that cinacalcet be funded on the Pharmaceutical Schedule with a high priority subject to the following access restriction in Section B and H of the Pharmaceutical Schedule:

> Special Authority for Subsidy
> Initial application only from a nephrologist or endocrinologist. Approvals valid for 12 months for applications meeting the following criteria:
>
> Both:
> 1. Patient has severe secondary or tertiary hyperparathyroidism where patient is persistently hypercalcaemic despite optimal conventional therapy; and
> 2. Any of the following:
>   2.1. Parathyroidectomy is contraindicated;
>   2.2. Patient is symptomatic and is awaiting parathyroidectomy; or
>   2.3. Patient has calciphylaxis.
>
> Renewal only from a nephrologist or endocrinologist. Approvals valid for 12 months for applications meeting the following criteria:
>
> Both:
> 1. Patient has previously benefitted from cinacalcet treatment; and
> 2. Any of the following:
>   2.1. Parathyroidectomy remains contraindicated;
>   2.2. Patient is symptomatic and is still awaiting parathyroidectomy; or
>   2.3. Patient has calciphylaxis.

4.2 The Subcommittee **recommended** that PHARMAC seek further clinical advice from PTAC about whether primary hyperparathyroidism should be added as a funded indication for cinalcalcet in view of the advice from the Endocrinology Subcommittee.

4.3 The Decision Criteria particularly relevant to this recommendation are *(i) The health needs of all eligible people within New Zealand (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

4.4 The Subcommittee noted that in July 2008, PTAC considered a paper from PHARMAC staff regarding the use of cinacalcet for hyperparathyroidism. The Committee noted that an application has not been made by the supplier of this product, but that the Exceptional Circumstances (EC) Panel of PHARMAC had requested that PTAC review this product in light of the increasing number of EC applications which been received. At the time, PTAC recommended that cinacalcet remain accessible through the Hospital Exceptional Circumstances scheme, and not be listed in the Pharmaceutical Schedule.

4.5 The Subcommittee also noted that cinacalcet was reviewed by the Endocrinology Subcommittee in June 2014 and that subcommittee had recommended that cinacalcet be funded, restricted to endocrinologists and renal physicians subject to the following restriction criteria:

- Patient has severe unremitting secondary hyperparathyroidism not successfully treated surgically; or
- Patient has calciphylaxis; or
- Patient has severe bone pain not amenable to pain relief; and
- Patient's serum calcium level is ≥ 3 mmols.

4.6 The Subcommittee noted that PTAC reviewed the Endocrinology Subcommittee minutes at its recent November 2014 meeting and requested that the Nephrology Subcommittee consider cinacalcet at this meeting and provide an opinion regarding the role of cinacalcet in the management of patients with renal disease and secondary or tertiary hyperparathyroidism.

4.7 The Subcommittee noted that animal studies have shown that parathyroid hormone is associated with bone and non-bone related toxicities. Parathyroidectomy and cinacalcet have both been shown to reduce the development of myocardial interstitial fibrosis and arteriolar wall thickening in animal models of secondary hyperparathyroidism.

4.8 The Subcommittee noted that there were conflicting results from two studies (Cunningham et al. Kidney Int 2005;68(4):1793-1800 and Palmer et al. PLoS 2013; Med 10(4): e1001436. doi: 10.1371/journal.pmed.1001436). The Subcommittee noted that the Cunningham et al analysis of 4 similarly designed RCTs was more selective and it concluded that cinacalcet resulted in significant reductions in the risk of parathyroidectomy (RR 0.07, 95% CI 0.01-0.55), fracture (RR 0.46, 95% CI 0.22-0.95), and cardiovascular hospitalisation (RR 0.61, 95% CI 0.43-0.86) compared with placebo.

4.9 The Subcommittee also noted the results from the ADVANCE study (Raggi et al. Nephrol Dial Transplant 2011;26(4):1327-39) which was a RCT comparing the progression of vascular and cardiac valve calcification in 360 patients on dialysis with secondary hyperparathyroidism treated with either cinacalcet plus low-dose vitamin D sterols or flexible doses of vitamin D sterols alone. For the primary endpoint, cinacalcet was associated with lower increase of coronary artery Agatston calcification scores (24% versus 31%) but this was not statistically

significant (p= 0.073). The Subcommittee noted that increases in calcification scores were less in the aorta, aortic valves and mitral valves in the cinacalcet treatment arm but was only statistically significant in the aortic valves. The Subcommittee also noted that plasma parathyroid hormone (PTH), serum calcium and phosphorus and calcium phosphorus product levels were significantly different in patients in the cinacalcet arm.

4.10 The Subcommittee considered the results of the EVOLVE study (The EVOLVE trial investigators. N Engl J Med 2012, DOI: 10.1056/ NEJMoa1205624) which was a RCT comparing cinacalcet with placebo in patients with moderate to severe hyperparathyroidism undergoing haemodialysis. All patients could continue to receive conventional therapy like phosphate binders and vitamin D sterols. The Subcommittee noted that the study reported that cinacalcet did not significantly reduce the risk of death or major cardiovascular events in patients with moderate to severe secondary hyperparathyroidism. Patients treated with cinacalcet had numerically lower rates of calciphylaxis (0.3%) when compared to patients in the placebo arm (0.9%).

4.11 The Subcommittee noted that cinacalcet treatment has been shown to enable achievement of Kidney Disease Quality Outcomes Initiative (KDQOI) targets in 1136 patients enrolled in three RCTs of cinacalcet (Moe et al. Kid.Int. 2005 (67): 760-771).

4.12 The Subcommittee considered that the available clinical evidence supports that:

- cinacalcet lowers PTH sustainably whilst patients are on treatment;
- enables achievement of calcium phosphate targets in a significant percentage of patients;
- reduces the requirement for parathyroidectomies; and
- reduces the incidence of calciphylaxis.

The Subcommittee considered that it remains unproven that cinacalcet reduces mortality and cardiovascular events in patients. The available evidence also indicates that cinacalcet is associated with risks of hypocalcaemia, neoplasia, seizures, QT prolongation, ventricular arrhythmias, nausea and vomiting. The Subcommittee noted that there are higher rates of renal failure and hyperparathyroidism in Māori.

4.13 The Subcommittee noted that the restriction criteria for cinacalcet in Australia were fairly liberal. Following the publication of the EVOLVE study, the Pharmaceutical Benefits Advisory Committee requested the supplier to either reduce cinacalcet's price, as at that price it was not cost-effective, or submit a submission for a more targeted population to improve the treatment's cost-effectiveness.

4.14 Given that it remains unproven that cinacalcet improves survival or cardiovascular outcomes, the Subcommittee considered that cinacalcet should

be targeted to patients with more severe disease who are likely to gain immediate or longer term symptomatic benefit including a reduction in pain, increase in function or amelioration of calciphylaxis. The Subcommittee considered that parathyroidectomy is an efficacious treatment but in some patients, surgery is not a treatment option due to patient comorbidities or tissue/gland location makes it inoperable. The Subcommittee also noted that cinacalcet could be useful for patients in whom parathyroidectomy is contraindicated and they are being optimised for renal transplant. Members noted that the cost of transplant was less than dialysis.

The Subcommittee considered that calcium and PTH levels should not be specified in the eligibility criteria for cinacalcet as those levels would not actually limit patient numbers. The Subcommittee noted that if cinacalcet was funded subject to the restriction criteria it had recommended, about 5% of dialysis patients would qualify for treatment, which would be about 200 to 250 patients per year. The Subcommittee considered 60mg daily would be the average dose of cinacalcet for this patient group.

4.15 The Subcommittee noted that cinacalcet could be useful in patients with primary hyperparathyroidism but considered that it would be more appropriate to seek advice from other clinical specialties that treat that disorder.

5 Sodium thiosulfate in calciphylaxis

Application

5.1 The Subcommittee noted a clinician funding application for sodium thiosulfate in calciphylaxis in Part II of Section H of the Pharmaceutical Schedule.

Recommendation

5.2 The Subcommittee **recommended** that sodium thiosulfate remain listed in Part II of Section H of the Pharmaceutical Schedule without restriction criteria.

5.3 The Decision Criteria particularly relevant to this recommendation are *(i) The health needs of all eligible people within New Zealand (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

5.4 The Subcommittee noted that when the Hospital Medicines List came into effect from 1 July 2013, sodium thiosulfate was listed without any access restrictions.

The access to the treatment previously had the oversight of local medicines committees. The Subcommittee noted that the Clinical Director of a DHB has asked that PHARMAC assess the cost-effectiveness of sodium thiosulfate in calciphylaxis, given the high cost and relative paucity of clinical evidence. The Subcommittee noted that PHARMAC then sought a funding application for sodium thiosulfate in this indication for review by this Subcommittee and PTAC.

5.5 The Subcommittee considered that calciphylaxis is a rare, severe, lethal disorder associated with significant pain and is very difficult to manage. Every year, about 1-2 patients develop this disorder in New Zealand. Calciphylaxis occurred more commonly in patients with diabetes and therefore would potentially disproportionately affect Maori. Currently, these patients are treated with sodium thiosulfate dosed at 25 mg intravenously, three times per week for an average period of 6 months. Other treatments include surgical debridement and oxygen therapy. The Subcommittee considered that patients with lesions on their trunk have a poorer prognosis than those with lesions on their limbs.

5.6 The Subcommittee considered that there is a very poor level of evidence for sodium thiosulfate with case reports and reviews with no randomised controlled trials (RCTs). The Subcommittee considered that it is unlikely that the evidence base would improve for the treatment in this indication. The Subcommittee noted that recent case reports indicate that sodium thiosulfate has therapeutic effect in calciphylaxis. Although the level of evidence is poor, there is currently no other more effective treatment in this area of high clinical need. The Subcommittee noted that because of the severity of the disorder, these patients are very unwell and would require significant hospital resource and care if the condition was not treated.

5.7 The Subcommittee considered that sodium thiosulfate should remain listed in Part II of Section H for patients with calciphylaxis. The Subcommittee considered that there is no financial benefit in restricting access to the treatment via restriction criteria in hospitals as it is unlikely that there is inappropriate use of the treatment currently.

6 Benefiber

Application

6.1 The Subcommittee noted a clinician funding application for Benefiber, a wheat dextrin soluble fibre supplement for the management of constipation in for patients with chronic kidney disease (grade 4 and 5) including those on peritoneal dialysis.

Recommendation

6.2 The Subcommittee **recommended** that the application to fund Benefiber is declined.

6.3 The Decision Criteria particularly relevant to this recommendation are *(i) The health needs of all eligible people within New Zealand (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

6.4 The Subcommittee noted the Lee et al study (Renal Soc Aust J 2011; 7(3): 122-129) which was provided in the application. The Subcommittee noted that the application states that Benefiber is preferred because it is associated with no drug interactions, however the Subcommittee noted that this is likely to be overstated given the lack of evidence to support that claim. The Subcommittee considered that Konsyl-D (ispaghula) is a funded alternative treatment. The Subcommittee noted that the claim of multiple drug interactions with ispaghula is unsubstantiated. It may interact with lithium but other interactions are unclear.

6.5 The Subcommittee considered that Konsyl-D had a similar therapeutic effect to Benefiber for the treatment of constipation. The Subcommittee noted that the application also supported the use of Benefiber over Konsyl-D due to its lower potassium content. The Subcommittee considered that the potassium content in Konsyl-D is very low and unlikely to result in significant effect in patients with renal failure. The Subcommittee however noted that Benefiber is potentially more palatable than Konsyl-D and had a lower sugar content.

6.6 The Subcommittee noted that Benefiber is significantly more expensive than Konsyl-D and the additional cost of funding the treatment is not justifiable based on the poor level of evidence currently available to support the use of Benefiber over Konsyl-D. The Subcommittee considered that it would be difficult to restrict the funding of Benefiber to just patients with chronic kidney disease as it would be viewed as a more favourable product for all patients who currently require a bulk-forming laxative. Therefore, the funding of Benefiber would present significant fiscal risk as it would be widely used.

7 Rituximab in MPO-ANCA positive vasculitis

Application

7.1 The Subcommittee noted that PHARMAC received a funding application from the New Zealand Rheumatology Association (NZRA) for the funding of rituximab with anti-neutrophil cytoplasm antibody (ANCA) associated vasculitides.

Recommendation

7.2 The Subcommittee **recommended** that the access criteria for rituximab in ANCA associated vasculitis is amended as follows (deletions in strikethrough, additions in bold):

Initiation - ANCA associated vasculitis
Limited to 4 weeks' treatment
All of the following:
1. Patient has been diagnosed with ANCA associated vasculitis*; and
~~2. Either:~~
   ~~2.1. Patient does not have MPO-ANCA positive vasculitis*; or~~
   ~~2.2. Mycophenolate mofetil has not been effective in those patients who have MPO-ANCA positive vasculitis*; and~~
3. The total rituximab dose would not exceed the equivalent of 375 mg/m^2 of body-surface area per week for a total of 4 weeks; and
4. Any of the following:
   4.1. Induction therapy with daily oral or pulse intravenous cyclophosphamide has failed to achieve ~~complete absence~~ **significant improvement** of disease after at least 3 months; or
   4.2. Patient has previously had a cumulative dose of cyclophosphamide >15 g or a further repeat 3 month induction course of cyclophosphamide would result in a cumulative dose >15 g; or
   4.3. Cyclophosphamide and methotrexate are contraindicated; or
   4.4. Patient is a female of child-bearing potential; or
   4.5. Patient has a previous history of haemorrhagic cystitis, urological malignancy or haematological malignancy.

Note: Indications marked with * are Unapproved Indications.

Continuation - ANCA associated vasculitis
Limited to 4 weeks' treatment

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

Note: Indications marked with * are Unapproved Indications.

7.3 The Decision Criteria particularly relevant to this recommendation are *(i) The health needs of all eligible people within New Zealand (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; and (vi)*

The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.

Discussion

7.4 The Subcommittee noted a request from PHARMAC and PTAC for clinical advice from this Subcommittee on whether rituximab is a more efficacious treatment than mycophenolate mofetil in patients with MPO-ANCA positive vasculitis. The Subcommittee noted that currently, patients with MPO-ANCA positive vasculitis are required to trial mycophenolate mofetil before having funded access to rituximab. The Subcommittee noted that this funding application has been reviewed by PTAC on multiple occasions.

7.5 The Subcommittee noted that granulomatosis with polyangiitis (GPA) was more prevalent in New Zealand compared to microscopic polyangiitis (MPA) and therefore PR3-ANCA positive disease was more common than MPO-ANCA positive disease (Gibson et al. Rheumatology 2006;45: 624–628). Treatments of these vasculitides involve induction, maintenance of remission and relapse treatment and the aim is to suppress inflammation and reduce levels of autoantibodies. Currently, induction therapy involves treatment with high dose corticosteroids and cyclophosphamide. There is a high rate of relapse (about 50%) and treatments during relapse include pulse IV cyclophosphamide followed by azathioprine. The Subcommittee however noted that there is a risk of significant toxicity with prolonged cyclophosphamide use including infections, cytopenias, malignancies, infertility and bladder toxicity.

7.6 The Subcommittee noted the results from the RITUXVAS (Jones et al. NEJM 2010; 363 (3):211-220) and RAVE studies (Stone et al. NEJM 2010; 363 (3):221-232 and Specks. NEJM 2013; 369: 417-427). The Subcommittee considered that the studies for rituximab in ANCA-associated vasculitis (AAV) involved small numbers of patients with relatively short follow-up times. The Subcommittee also noted that the superiority of rituximab over conventional treatments like cyclophosphamide has not been shown on vasculitis-related damage for example, loss of renal function, increased mortality and reduced quality of life. The Subcommittee considered that it is not clear that rituximab is safer in the short or long term when compared to cyclophosphamide. It is also not clear that rituximab works as quickly as cyclophosphamide to preserve glomeruli.

7.7 The Subcommittee noted that the National Institute for Health and Care Excellence (NICE) recommends that rituximab should be considered a treatment option for inducing remission in adults with AAV and have generalised severe disease if cyclophosphamide is contraindicated or not clinically appropriate (NICE technology appraisal guidance, TA 308, published March 2014).

7.8 The Subcommittee noted the results of the studies comparing mycophenolate mofetil to conventional therapy in ANCA vasculitis. The Subcommittee noted that in the Hiemstra et al study (JAMA. 2010;304(21):2381-2388), relapses were more common in the mycophenolate mofetil group (42/76 patients) compared with the azathioprine group (30/80 patients) (unadjusted hazard ratio for mycophenolate mofetil of 1.69 (95% CI 1.06-2.70; P=0.03). The Subcommittee

noted that there was no significant difference in the safety of the two treatments. The Subcommittee noted that there was also no evidence of difference between groups for the secondary outcomes of the Vasculitis Damage Index, glomerular filtration rates and proteinuria.

7.9 The Subcommittee noted the results of the Hu et al study (Nephrol Dial Transplant 2008;23: 1307–1312) which involved 28 patients with MPO-ANCA positive vasculitis. The Subcommittee noted that when compared to intermittent cyclophosphamide, mycophenolate mofetil was associated with lower Birmingham Vasculitis Activity Scores (BVAS) (0.2 ± 0.89 versus 2.6 ± 1.7, $P < 0.05$). In the intent-to-treatment analysis, 14 of 18 patients (77.8%) treated with mycophenolate mofetil and 8 of 17 patients receiving CTX (47.1%) had complete remission with an absolute difference of 30.7%.

7.10 The Subcommittee also noted that the Silva et al study (Clin J Am Soc Nephrol 2010;5:445–453) which investigated the efficacy of mycophenolate in patients with MPA and mild to moderate renal involvement. The Subcommittee noted that 13 of 17 patients enrolled achieved the primary outcome, and 4 failed because of insufficient response, relapse, or mycophenolate intolerance. Twelve patients remained in remission through month 18, renal function remained stable, and proteinuria improved.

7.11 The Subcommittee considered that the current available clinical studies for mycophenolate in vasculitis involved very small patient numbers. The Subcommittee noted that the MYCYC study results have not been published (Jones et al 2013. http://dx.doi.org/10.1016/j.lpm.2013.02.067) and would potentially shed more light on the efficacy and safety of mycophenolate when compared to cyclophosphamide. In the primary analysis, the study was unable to demonstrate that mycophenolate is non-inferior to cyclophosphamide for remission induction at six months in newly diagnosed AAV.

7.12 The Subcommittee considered that there is currently insufficient evidence to support that mycophenolate mofetil is an appropriate treatment in patients with MPO-ANCA positive vasculitis and severe disease. The Subcommittee also considered that there is insufficient evidence to support that it would be appropriate to treat mild/moderate disease differently to severe disease. The Subcommittee considered that at this time, the evidence base for rituximab in MPO-ANCA vasculitis is stronger than that for mycophenolate mofetil. The Subcommittee considered that it would also be clinically appropriate to amend criteria 4.1 to enable rituximab to be used in patients where cyclophosphamide has failed to achieve significant improvement because complete absence of disease is very rare in these clinical situations. The Subcommittee estimates that an additional 50 patients per year would access rituximab if the criteria were amended as it has recommended.