

**PTAC meeting held on 8 & 9 May 2014**

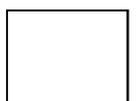
**(minutes for web publishing)**

PTAC minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2008*.

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

PTAC may:

- (a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
- (b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or
- (c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.



**Record of the  
Pharmacology and Therapeutics Advisory  
Committee Meeting  
Held on 8 & 9 May 2014**

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## 1. Matters Arising

- 1.1. Analgesic Subcommittee minutes for methoxyflurane
- 1.2. The Committee noted that it had not previously commented on the Analgesic Subcommittee's April 2012 recommendation to fund methoxyflurane in the community with a medium priority for patients undergoing painful procedures with an expected duration of less than one hour.
- 1.3. The Committee considered that it needed to review the evidence, including safety data, presented to the Analgesic Subcommittee, as well as any new evidence published since the April 2012 review, before making a recommendation in relation to community funding for methoxyflurane.
- 1.4. The Committee considered that it would be important to review the efficacy evidence and safety information in the context of alternative potential treatment options for the relevant uses (e.g. burns dressings changes, ambulance use, ski patrol use), including both funded options (e.g. opioids, including intranasal fentanyl) and currently unfunded community options (e.g. ketamine and nitrous oxide).
- 1.5. The Committee considered that it was important to ensure that patients undergoing painful procedures in the community have access to as effective pain control as they would if they were undergoing the same procedures conducted in hospitals.

## 2. Subcommittee Minutes

### ***Special Food Subcommittee – 5 December 2014***

- 2.1. The Committee noted and accepted items 1 to 14 of the minutes
- 2.2. Regarding items 6 to 10 inclusive, the Committee had extensive discussion relating to the use of thickened fluids as a management technique for patients with dysphagia. The Committee noted that currently, only patients with motor neurone disease have funded access to subsidised food/fluid thickeners in the community. The Committee noted the current restrictions relating to the use of food/fluid thickeners in DHB hospitals. The Committee noted that aspiration pneumonia has a complex causal pathway, and dysphagia, although a substantial risk factor for aspiration pneumonia is not the only risk factor. The Committee noted that food/fluid thickeners are included as part of the management of dysphagia in international protocols. The Committee noted the evidence that had been provided to the Special Foods Subcommittee, in particular it noted a systematic review and evidence based recommendations on texture modified foods and thickened fluids for adults ( $\geq 18$  years) with oropharyngeal dysphagia by Andersen et al (eSPEN Journal, 8:2013:e127-134). The Committee noted that the Special Foods Subcommittee considered that there was some good strength and quality of evidence for the use of thickened fluids in order to prevent aspiration pneumonia in the acute phase of dysphagia. It also noted that the Special Foods Subcommittee considered there is no strong evidence for the use of thickened fluids in order to prevent aspiration pneumonia in patients with chronic dysphagia and that the Special Food Subcommittee considered that this chronic phase of dysphagia would be present in the community setting.
- 2.3. The Committee accepted the recommendations made by the Special Foods Subcommittee in relation to these items. The Committee **recommended** that patients who are currently receiving subsidised food/fluid thickener via Special Authority for use in the community, be 'grandparented' and continue to receive



subsidised food/fluid thickener. The Committee recommended that, should the recommendation to delist food/fluid thickeners from Section D of the Pharmaceutical Schedule be progressed, that extensive consultation is performed.

#### ***Cardiovascular Subcommittee – 27 February 2014***

- 2.4. The Committee noted and accepted items 1 to 6 of the minutes, with the exception of recommendations in relation to ranolazine (items 3.3 and 3.4) apixaban (item 5) and rivaroxiban (item 6).
- 2.5. Regarding items 3.3 and 3.4, the Committee noted its previous August 2012 recommendation that an additional treatment for refractory angina should be listed with a high priority, that this should be positioned after maximal treatment with first-line therapies (including beta-blockers, calcium channel antagonists and long-acting nitrates), that this could be either ranolazine or nicorandil (although preferably both), and that both are clinically preferable to perhexiline which should be the last-line product due to its increased monitoring requirements and potential for complications. The Committee noted that nicorandil was subsequently listed on the Pharmaceutical Schedule from 1 October 2012. The Committee now considered that the clinical need for another treatment for refractory angina is unclear.
- 2.6. The Committee declined the recommendation from the Cardiovascular Subcommittee to list ranolazine with a high priority. The Committee noted that it would be happy to review the recommendation should new clinical evidence or information relating to the requirement for an additional treatment for refractory angina become available.
- 2.7. The Committee deferred making a recommendation on the Cardiovascular Subcommittee minutes pertaining to apixaban and rivaroxaban for the various indications applied for. The Committee noted that funding applications for both of these products were to be reviewed at this meeting.

#### ***Immunisation Subcommittee – 10 February 2014***

- 2.8. The Committee reviewed the minutes from the February 2014 Immunisation Subcommittee meeting and noted and accepted all items.

#### ***Dermatology Subcommittee – 9 December 2013***

- 2.9. The Committee noted and accepted items 2.1.1 to 2.1.25 with the exception of the item 2.1.6 regarding the PASI score criteria to treat chronic plaque psoriasis, items 2.1.12 and 2.1.13 in relation to TNF inhibitors to treat Beçhets disease and item 2.1.16 regarding the application of unsubsidised galenicals used for compounding.
- 2.10. The Committee noted that the Dermatology Subcommittee had recommended the listing of TNF inhibitors for the treatment of patients with severe Beçhets disease with a medium priority.
- 2.11. Members considered their previous recommendation of a medium priority and considered as an action point that the application still required review by the Ophthalmology Subcommittee for their advice on specific Special Authority Criteria and whether the Ophthalmology Subcommittee had a preference for the specific TNF(s) to be funded.
- 2.12. The Committee noted paragraphs 6.8 to 6.17 of the Dermatology Subcommittee's minutes and considered that PHARMAC should review the numbers of patients

eligible (based on previous applications) were the Special Authority criteria using adalimumab to treat chronic plaque psoriasis to change to a PASI score of from 15 to 10. Members considered that the patient numbers be reviewed as an action point, and recommended that if patients were few then the Special Authority should be changed. Members further considered however that if patient numbers were not small then this would require further full review by PTAC.

- 2.13. Members **recommended** that PHARMAC investigate the potential to allow an unsubsidised galenical to be added to a compounded mixture and only have the unfunded component non-subsidised, rather than having the entire compounded product unsubsidised.

### ***Diabetes Subcommittee – 11 December 2013***

- 2.14. The Committee reviewed the minutes from the December 2013 Diabetes Subcommittee meeting and noted and accepted all items.

### ***Anti-Infective Subcommittee – 17 April 2014***

- 2.15. The Committee reviewed the minutes from the April 2014 Anti-Infective Subcommittee meeting and noted and accepted all items.

- 2.16. The Committee noted the application for ceftaroline would be considered at this meeting.

## **3. Food /Fluid thickeners and pre-thickened fluids**

Refer to the Special Foods Subcommittee minutes.

## **4. Rivaroxaban for the treatment of venous thromboembolism, secondary prophylaxis of venous thromboembolism and stroke prevention in non-valvular atrial fibrillation**

### **Application**

- 4.1. The Committee noted the application from Bayer for the listing of rivaroxaban (Xarelto) in Sections B and H of the Pharmaceutical Schedule for three indications: treatment of venous thromboembolism (VTE), secondary prophylaxis of VTE and stroke prevention in non-valvular atrial fibrillation (AF).

### **Recommendation**

- 4.2. The Committee **recommended** that rivaroxaban be listed in Sections B and H of the Pharmaceutical Schedule for the treatment of VTE, secondary prophylaxis of VTE and stroke prevention in non-valvular AF only if cost-neutral to dabigatran.
- 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; 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 Committee noted that it had previously reviewed the funding application for rivaroxaban in these indications and had deferred making a recommendation until the application was reviewed by the Haematology, Cardiovascular and Neurological Subcommittees. The Committee noted the recommendations of the three Subcommittees relating to rivaroxaban in these indications.

### ***Treatment of VTE and secondary prophylaxis of VTE***

- 4.5. The Committee noted that dabigatran and apixaban are not yet Medsafe-registered for these indications but their registrations are expected in the near future. The Committee noted that there were no head-to-head studies comparing rivaroxaban, apixaban and dabigatran in these two indications. The Committee noted the findings of a number of systematic reviews and meta-analyses that compared these three agents. The Committee considered that when compared with low molecular weight heparin (LMWH) bridging therapy and warfarin, the available evidence indicates that rivaroxaban could be associated with reduced major bleeding with a relative risk of 0.55 (95% confidence interval (CI) 0.38 to 0.81) (Kang et al. *Thromb Res* 2014. <http://dx.doi.org/10.1016/j.thromres.2014.03.035>). The Committee noted this systematic review reported there was no evidence of clinical benefit for mortality or VTE recurrence with rivaroxaban when compared with LMWH bridging therapy and warfarin.
- 4.6. From indirect comparisons with dabigatran (Kang et al. *Thromb Res* 2014. <http://dx.doi.org/10.1016/j.thromres.2014.03.035>; van der Hulle et al. *J Thromb Haemost* 2014;12:320-8), the Committee noted that there were no reported differences between rivaroxaban and dabigatran for mortality and VTE recurrence, but these studies suggest that rivaroxaban may be associated with less bleeding. The Committee also noted that Loke et al (*Br J Clin Pharmacol* 2014, doi: 101111/bcp.12376 [Epub ahead of print]) reported that dabigatran was associated with an increased risk of acute coronary syndromes (ACS) when compared with other novel oral anticoagulants (NOACs). The Committee noted that of these NOACs, only dabigatran has been compared with warfarin for secondary prevention. Dabigatran has been reported to be associated with equivalent efficacy to warfarin in terms of VTE prevention but associated with lower rates of bleeding (Schulman et al. *N Engl J Med* 2013;368:709-18).
- 4.7. The Committee noted that the above indirect comparisons by van der Hulle et al. and Kang et al. reported no differences between rivaroxaban and apixaban for mortality, VTE recurrence or bleeding.
- 4.8. The Committee noted that all the NOACs, including rivaroxaban, do not have proven reversal agents at this time, which is a safety risk. The Committee also noted that a large proportion of rivaroxaban, approximately one third, still relied on direct renal clearance.
- 4.9. The Committee considered that the population most likely to benefit from rivaroxaban in the treatment and secondary prophylaxis of VTE are those patients who are intolerant or contraindicated to warfarin, or in whom frequent blood tests for INR (international normalised ratio) monitoring is not possible. The Committee however noted that LMWH or dabigatran (when it obtains Medsafe registration for this indication), may be treatment options for these patients.

- 4.10. The Committee considered that on balance there would be clinical benefit in listing one Factor Xa inhibitor in addition to dabigatran as there is significant intolerance to dabigatran due to gastric irritation and also if evidence emerges for a reversal agent that is Factor Xa specific. The Committee considered that, from the available evidence, apixaban appeared to be the better agent when compared with rivaroxaban, because a smaller proportion of apixaban is renally cleared and there is some weak indirect evidence from network meta-analyses that apixaban may be associated with a lower risk of bleeding when compared with the other NOACs.
- 4.11. The Committee made the following comments in response to Bayer's rebuttal of points raised by PTAC during the review of rivaroxaban at its November 2012 meeting:
- 4.12. The Committee considered that it was not possible to judge if the numerical variance in the proportion of patients with creatinine clearance (CrCl) <30ml/min in the EINSTEIN-DVT treatment groups influenced the outcome of the study, because no sensitivity analysis by CrCl was presented.
- 4.13. The Committee noted that recent meta-analyses do indicate that rivaroxaban and apixaban are associated with less major bleeding when compared with bridging LMWH with warfarin (Kang et al. *Thromb Res* 2014. <http://dx.doi.org/10.1016/j.thromres.2014.03.035>). The Committee noted that there is a risk with Type 1 error rate inflation with meta-analyses. The Committee also noted that van der Hulle et al paper (*J Thromb Haemost* 2014; 12: 320-8) indicated that the absolute risk difference for major bleeding between these NOACs and vitamin K antagonists was small, -0.67% (95% CI -1.13 to -0.21) with a high number-needed-to-treat (NNT) of 149 (95% CI 88-476).
- 4.14. In regards to whether the variation in the time in therapeutic range (TTR) would have influenced the efficacy outcome in the first three weeks of the EINSTEIN-DVT study, the Committee considered that it was not possible to be certain because there has been no published information on meta-regression attempts for this factor.
- 4.15. The Committee considered that the question of whether rivaroxaban reduces the rates of post-thrombotic syndrome (PTS) is unresolved, simply because this was not addressed by the available clinical trial evidence.
- 4.16. The Committee considered that when compared to the body of evidence we have currently for bridging LMWH and warfarin, there is not the same long-term experience with rivaroxaban at this time.

### ***Stroke prevention in non-valvular AF***

- 4.17. The Committee noted that there were no head-to-head studies comparing rivaroxaban, apixaban and dabigatran in this indication. The Committee noted the results of a number of systematic reviews and meta-analyses comparing these three agents in AF. When compared with warfarin, the Committee considered that there was no robust evidence to confirm that rivaroxaban was associated with better efficacy for the prevention of stroke and systemic embolism. The Committee noted that the network meta-analysis by Dogliotti et al (*Heart* 2014;100:396-405) did suggest that the point estimates for rivaroxaban are better for this outcome. In terms of overall bleeding, the Committee noted that available studies reported no differences between rivaroxaban and warfarin in the AF indication, but the Committee noted that there was some evidence that rivaroxaban was associated with a lower risk of bleeding in the VTE studies against LMWH and warfarin.

- 4.18. Based on indirect comparisons, the Committee considered that the efficacy of rivaroxaban was similar to dabigatran for the prevention of stroke and systemic embolism. The Committee noted that, unlike dabigatran, rivaroxaban was not associated with an increased risk of ACS (Loke et al. *Br J Clin Pharmacol* 2014, doi: 101111/bcp.12376 [Epub ahead of print]). The Committee considered that although the overall risk of bleeding seems to not differ between the NOACs, rivaroxaban and dabigatran appear to be associated with a higher risk of gastrointestinal bleeding whereas apixaban is not. The Committee noted that although rivaroxaban is not primarily excreted renally, dose adjustment is still required in renal failure.
- 4.19. The Committee considered that there does not appear to be a difference in efficacy between rivaroxaban and apixaban for the prevention of stroke or systemic embolism. The Committee noted that the results from the study of apixaban versus aspirin (Connolly et al. *N Engl J Med* 2011;364:806-17) weakly support apixaban over the other NOACs because of its lower bleeding risk.
- 4.20. The Committee considered that the patient population most likely to benefit from rivaroxaban in this indication are those patients who are intolerant or contraindicated to warfarin, or in whom frequent blood tests for INR (international normalised ratio) monitoring is not possible. The Committee considered that there would be clinical benefit in listing one Factor Xa inhibitor in addition to dabigatran (a direct thrombin inhibitor) for patients with AF.
- 4.21. The Committee made the following comments in response to Bayer's rebuttal of points raised by PTAC during the review of rivaroxaban at its November 2012 meeting:
- 4.22. The Committee maintains that there is no strong evidence of the NOACs' superiority over vitamin K antagonists although point estimates favour NOACs, as summarised by the Dogliotti et al network meta-analysis (*Heart* 2014;100:396-405) which supersedes a single trial result.
- 4.23. The Committee noted that the network meta-analysis by Dogliotti et al (*Heart* 2014;100:396-405) reported that there was no difference in combined major bleeding between the NOACs and vitamin K antagonists. The Committee however also noted that Culebras et al (*Neurology* 2014; 82:716-24) reported some increased gastrointestinal bleeding with rivaroxaban and dabigatran but less intracranial bleeding for all the NOACs when compared with vitamin K antagonists.
- 4.24. The Committee noted the ITT results for all the pre-specified outcomes in the ROCKET study (Hankey et al. *Lancet Neurol* 2012;11:315-22). The Committee noted that one out of the eighteen outcomes reported was significant at 0.012, but considered that Type 1 error rate inflation could account for this.
- 4.25. The Committee noted that the combined subgroup analysis by Gómez-Outes et al. (*Thrombosis* 2013; <http://dx.doi.org/10.1155/2013/640723>) could not find evidence of a subgroup effect by previous stroke/transient ischaemic stroke or TTR. The Committee considered that the effect of NOACs is likely the same in these two subgroups of patients. The Committee also considered that there is no evidence to support that the efficacy of the NOACs is influenced by whether patients have congestive heart failure.
- 4.26. The Committee considered that the higher rate of primary events amongst patients who transitioned from rivaroxaban compared with those who transitioned from warfarin (Patel et al. *N Engl J Med*. 2011;365(10):883-91 online supplementary files) seems to be a result of the clinical trial design and its relevance to actual clinical use is unclear.

- 4.27. The Committee maintained that at this time, the body of clinical evidence for all the NOACs is less than that for the vitamin K antagonists. The Committee noted also that at this time, there is no randomised controlled trial evidence for the management of patients on NOACs with reversal agents.
- 4.28. The Committee considered that there was no clinical need to list rivaroxaban with a Special Authority restriction given dabigatran is listed without such restriction currently.
- 4.29. The Committee considered that it would be beneficial to list a Factor Xa inhibitor because there was currently an unmet clinical need for patients who are intolerant to dabigatran. The Committee noted that the Haematology Subcommittee had concerns that funding too many NOACs in addition to dabigatran could increase the chances of prescribing and dispensing errors. The Committee acknowledged that this could pose a safety risk and that funding only one additional NOAC could reduce this risk. However, the Committee noted that clinicians and prescribers have a role in ensuring the NOACs are prescribed safely regardless of the number of funded NOACs. The Committee considered that if PHARMAC decided to list more than one other NOAC in addition to dabigatran, it would be important to make sure good information was available (e.g. about dosages in different indications for the different agents and dosing in patients with renal impairment) to help mitigate the risk of prescribing and dispensing errors.
- 4.30. The Committee considered that it would be difficult to run a competitive process for a Factor Xa inhibitor because possible brand switches required at the end of each competitive process would be complex given these agents are not directly interchangeable. The Committee considered that although apixaban is somewhat favoured over rivaroxaban, the cost-effectiveness of both medicines should be taken into account when funding is considered.

## 5. **Apixaban for venous thromboembolism prophylaxis following major orthopaedic surgery and stroke prevention in non-valvular atrial fibrillation**

### **Application**

- 5.1. The Committee noted the application from Pfizer for the listing of apixaban (Eliquis) in section B and H of the Pharmaceutical Schedule venous thromboembolism (VTE) prophylaxis following major orthopaedic surgery and stroke prevention in non-valvular atrial fibrillation (AF).

### **Recommendation**

- 5.2. The Committee **recommended** that apixaban be listed in Sections B and H of the Pharmaceutical Schedule for VTE prophylaxis following major orthopaedic surgery only if cost-neutral to rivaroxaban and dabigatran.
- 5.3. The Committee **recommended** that apixaban be listed in Sections B and H of the Pharmaceutical Schedule for stroke prevention in non-valvular AF with a low priority.
- 5.4. The Decision Criteria particularly relevant to these recommendations 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 publically 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**

- 5.5. The Committee noted the recommendations of the Haematology, Cardiovascular and Neurological Subcommittees in relation to apixaban in these indications.

### ***VTE prophylaxis following major orthopaedic surgery***

- 5.6. The Committee considered that the clinical evidence provided for apixaban in this indication was of good strength and quality. The Committee considered that the available systematic reviews and meta-analyses (Cohen et al. *Clin Appl Thromb Hemost.* 2012;18:611-27, Gómez-Outes et al. *BMJ* 2012;344: e3675; Adam et al. *Ann Intern Med* 2013;159: 275-84) provide evidence that the novel anticoagulants (NOACs) are likely to be more efficacious than low molecular weight heparin (LMWH) but are likely to be associated with increased risks of bleeding. The Committee considered that there is not strong statistical evidence to distinguish between the novel oral anticoagulants (NOACs) but apixaban and rivaroxaban may be better for some outcomes when compared with LMWH whereas dabigatran appeared to be similar to LMWH. The Committee also considered that rivaroxaban may be associated with higher bleeding risks when compared with apixaban and dabigatran.
- 5.7. The Committee considered that there is currently no problem with access to or availability of alternative treatments for this indication, for example intermittent calf compression devices, LMWH, dabigatran, and rivaroxaban.

### ***Stroke prevention in non-valvular AF***

- 5.8. The Committee considered that the strength and quality of the evidence for apixaban in this indication to be good. The Committee noted that two grade 1+ studies at low risk of bias reported that apixaban was superior to aspirin alone and provided moderate evidence that it was superior to warfarin (Connolly et al. *N Engl J Med* 2011;364: 806-17; Granger et al. *N Engl J Med* 2011;365:981-92). The Committee noted that these studies also reported that apixaban was associated with slightly more bleeding when compared with aspirin but less bleeding when compared with warfarin.
- 5.9. The Committee considered that, based on network meta-analysis by Dogliotti et al (*Heart* 2014;100:396-405), there were no differences between the NOACs and warfarin in effects on stroke, systemic embolism, mortality or major bleeding; although the point estimates favoured the NOACs over warfarin. The Committee considered that there was no evidence that any particular subgroup of patient would benefit from NOACs versus warfarin (Gómez-Outes et al. *Thrombosis* 2013: 640723 doi <http://dx.doi.org/10.11555/2013/640723>).
- 5.10. The Committee considered that although the above Granger et al study reported that the incidence of stroke or systemic embolism with apixaban was lower compared with warfarin, the confidence intervals were relatively wide with a hazard ratio upper limit of 0.95. The Committee noted that the Dogliotti et al network meta-analysis reported no difference when apixaban was compared with dabigatran and rivaroxaban for the four key outcomes.
- 5.11. The Committee noted that it is recommended that the dose for apixaban be reduced for patients with renal impairment (serum creatinine >133 micromol/l), patients aged >80 years, and those with low body mass (Eliquis Medsafe

datasheet). The Committee also noted that its use is not recommended in patients with a creatinine clearance <25 ml/min.

- 5.12. The Committee noted the summary of 21 subgroup analyses provided in the funding application for apixaban in this indication. The Committee considered that the available evidence indicates that apixaban is equally effective as warfarin irrespective of age and renal function; however, the Committee noted the risk of Type 1 error with multiple subgroup analyses.
- 5.13. The Committee considered that the patient population most likely to benefit from apixaban in this indication are those patients who are intolerant or contraindicated to warfarin, or in whom frequent blood tests for INR (international normalised ratio) monitoring is not possible. The Committee considered that there would be clinical benefit in listing one Factor Xa inhibitor in addition to dabigatran for AF in the event evidence emerges for a reversal agent which is Factor Xa specific.
- 5.14. The Committee considered that there was no clinical need to list apixaban with a Special Authority restriction, given dabigatran is listed without such restriction currently.
- 5.15. The Committee considered that it would be beneficial to list a Factor Xa inhibitor because there was currently an unmet clinical need for patients who are intolerant to dabigatran. The Committee noted that the Haematology Subcommittee had concerns that funding too many NOACs in addition to dabigatran could increase the chances of prescribing and dispensing errors. The Committee acknowledged that this could pose a safety risk and that funding only one additional NOAC could reduce this risk. However, the Committee noted that clinicians and prescribers have a role in ensuring the NOACs are prescribed safely regardless of the number of funded NOACs. The Committee considered that if PHARMAC listed more than one other NOAC in addition to dabigatran, it would be important to make sure good information was available (e.g. about dosages in different indications for the different agents and dosing in patients with renal impairment) to help mitigate the risk of prescribing and dispensing errors.
- 5.16. The Committee considered that it would be difficult to run a competitive process for a Factor Xa inhibitor because possible brand switches required at the end of each competitive process would be complex given these agents are not directly interchangeable. The Committee considered that although apixaban is somewhat favoured over rivaroxaban, the cost-effectiveness of both medicines should be taken into account when funding is considered. The Committee noted that apixaban has advantages clinically over rivaroxaban because there is direct clinical trial evidence comparing apixaban with aspirin in AF and apixaban is less dependent on renal excretion than rivaroxaban.
- 5.17. The Committee noted that some aspects of the quality of the funding application was poor with repetition of material and inclusion of non-English language publications without adequate translations.

The minute of this item originally approved by PTAC was amended to correct a small number of factual matters at its November 2014 meeting. The version above is the corrected version.

## 6. Ivacaftor application for funding for the treatment of cystic fibrosis

### Application

The Committee reviewed an application from Vertex Pharmaceuticals (Australia) Pty Ltd for the listing of ivacaftor on the Pharmaceutical Schedule for the treatment of patients with cystic fibrosis.

### Recommendation

- 6.1. The Committee deferred making a recommendation until data is available from the clinical trials evaluating ivacaftor in combination with lumacaftor (VX-809) and until PHARMAC have completed further cost utility analysis on three discreet groups of patients – asymptomatic, bridge to transplant, and advanced disease stage.

### Discussion

- 6.2. The Committee noted that cystic fibrosis (CF) is a genetic defect of a chloride channel regulator (the cystic fibrosis transmembrane conductance regulator or CFTR) resulting in the dehydration of secretions which leads to sticky viscous secretions. Members noted that there are more than 1600 CFTR gene mutations and a wide spectrum of disease severity that cannot necessarily be predicted from genotype. Members noted that approximately 4% of CF patients worldwide have the Class III (gating) mutation, G551D on at least one allele. This type of mutation results in a CFTR protein that is present in the apical cell membrane but displays greatly reduced chloride transport. The Committee noted that about 26 of the 430 cystic fibrosis patients in New Zealand have the G551D gene.
- 6.3. The Committee noted ivacaftor is a CFTR potentiator that increases chloride channel function by facilitating CFTR opening. Members noted that ivacaftor is registered for use in New Zealand for the treatment of CF patients aged 6 years and older who have a G551D mutation in the CFTR gene with a recommended dose of 150 mg taken orally every 12 hours with a fat containing snack or meal.
- 6.4. The Committee noted there is evidence of a moderate quality of a large therapeutic effect essentially from two main double blind randomised trials – STRIVE (Ramsey et al NEJM 2011;365:1663-72) and ENVISION (Davies et al Am J Respir Crit Care Med 2013;187,11:1219-1225), both being company-designed and -sponsored.
- 6.5. The Committee noted that of the 161 patients over the age of 12 years enrolled in the STRIVE study, 83 were randomised to ivacaftor, 78 to placebo, treated for 48 weeks. The primary endpoint was a change in FEV<sub>1</sub> at 24 weeks. The absolute change was a 10.4% increase in FEV<sub>1</sub> with treatment compared with -0.2% with placebo (p<0.001) at 24 weeks, with improvement seen by day 15 and maintained through week 48. There were reductions in exacerbations (47 vs 99), hospitalisations (21 vs 31) and days in hospital for exacerbations (3.9 vs 4.2); an increase in CFQ-R scores in the treatment group compared with a decrease of 2.7 points in the placebo group; weight gain (3.1 kg vs 0.4 kg), although this appeared to plateau at week 16; and a change in sweat chloride. The incidence of adverse events through to week 48 was similar in the two groups. The ivacaftor group had a higher level of adverse events leading to interruption but not discontinuation of the drug than placebo (13% vs 6%). More placebo patients discontinued treatment than those on ivacaftor (5% vs 1%). The Committee noted that 70% of patients in this study were also on dornase alfa.

- 6.6. The Committee noted 52 children aged between 6 and 12 (mean age 8.9 years) were enrolled in the EVISION study and were evenly divided between ivacaftor and placebo. Again, the primary endpoint was the absolute change from baseline through week 24 in the percent of predicted FEV<sub>1</sub>. An improvement was seen by day 15, by week 24 there was an absolute improvement of 12.6% compared with 0.1% in placebo (p<0.001), and 10.7% vs 0.7% at week 48 (p<0.001). Further benefits were a relative increase of 2.8 kg in body weight compared with the placebo group at week 48, an increase in the CFQ-R score of 6.3 points vs 0.3 points, and a significant decrease in sweat chloride concentrations. Exacerbations were not significantly different between the two groups, and the incidence of adverse events were similar.
- 6.7. The Committee noted interim data from the unpublished PERSIST study, which is an unblinded extension of STRIVE and ENVISION with 192 patients active at 96 weeks. All subjects received ivacaftor 150 mg BD regardless of previous treatment. While immature, the data suggests the change in FEV<sub>1</sub> persists in those patients who were previously treated with ivacaftor and the FEV<sub>1</sub> change in the placebo group is similar to that seen in the treated group.
- 6.8. The Committee noted that there is a lack of maturity in the RCT data that makes estimates of long term effects uncertain. Low patient numbers in the initial clinical trials also adds to the uncertainty.
- 6.9. The Committee noted the dose-defining study by Accurso et al study (Study 101, NEJM 2010). Participants were aged 18 years and over, with at least one G551D-CFTR mutation and an FEV<sub>1</sub> ≥ 40%. In Part 1 of the study, patients were randomly assigned to receive 25 mg, 75 mg or 150 mg ivacaftor or placebo. The drug was administered during two 14 day periods separated by a washout. Part 2 involved new patients assigned 150 or 250 mg twice daily for 28 consecutive days. The reduction in FEV<sub>1</sub> percentage of predicted between the 75 mg BD and 150 mg BD treatment regimens was similar (10.0% and 10.5% respectively). The decision to proceed with the 150 mg BD protocol and stop using the 75 mg BD is not well explained. The results suggested that 75 mg BD may work just as well as the 150 mg BD recommendation which would reduce the cost of the treatment.
- 6.10. The Committee noted three patient studies: Hebestreit et al. J Cyst Fibrosis 2013;12:599-603; Wood et al Respirology Case Reports 2013;1(2):52-54; Barry et al Poster, Cystic Fibrosis Conference. All three reported on patients with severe disease treated with ivacaftor in clinical settings either under compassionate grounds or named patient programs.
- 6.11. The Committee noted that, unlike the above studies where around 60% of patients were taking dornase alfa, only approximately 90 of the 430 patients (21%) in New Zealand who have been diagnosed with cystic fibrosis are taking dornase alfa. The Committee noted that, outside of the main centres, in New Zealand there is a lack of multidisciplinary teams (physicians, dieticians and physiotherapists) to treat cystic fibrosis patients, which has had a detrimental effect on patients' treatment. The Committee considered this paucity of integrated multidisciplinary care had contributed to patients in New Zealand generally having greater morbidity than their counterparts in the UK and US (where patients have better access to multidisciplinary teams), and also greater morbidity than patients in the ivacaftor studies.
- 6.12. The Committee noted the improvements in FEV<sub>1</sub> seen in the clinical trials with dornase alfa (ref Cochrane review). At one month, reported in four trials, the mean difference from baseline in FEV<sub>1</sub> was 8.3%; at three months; reported in one trial it was 7.3%; at six months; reported in one trial it was 5.8%; at one year, reported in one trial it was 4.1%; and at two years reported in one trial it was 3.2%. At three

years, reported in one trial there was no significant difference, but patient numbers were small. The Committee considered the results indicated that dornase alfa has a similar initial effect compared with ivacaftor but that effect appears to wane quickly over time.

- 6.13. The Committee noted that while ivacaftor appears to maintain an improvement of ~10% out to three years, what is not known is the effect on FEV<sub>1</sub> beyond that period of time. The Committee noted that by three years approximately half of the patients on ivacaftor had experienced an exacerbation which would have resulted in some loss of lung function. The Committee noted that the Respiratory Subcommittee had suggested that the rate of decline may be similar to non-CF bronchiectasis, which is approximately half the rate of CF patients.
- 6.14. The Committee considered that while ivacaftor represents a significant improvement in the treatment of cystic fibrosis, it is not a cure. Members considered that the data is too immature to determine survival benefit, but the reported apparent improvement at three years would imply it would not be unreasonable to expect improvement beyond that time. Members noted that ivacaftor would be given in combination with all the treatments that patients currently receive, expect for hypertonic sodium chloride, which would provide additional benefits over the current standard treatments. The Committee noted that following the improvement in a patient's FEV<sub>1</sub> of ~10% as seen in the clinical trials, it could be expected that FEV<sub>1</sub> would slowly decline in a similar way to that seen in patients with bronchiectasis.
- 6.15. The Committee noted that only patients with the G551-D-CFTR mutation gene would benefit from ivacaftor, although members noted that the FDA had recently extended the licence in the US to cover the eight additional mutations G178R, G551S, S549N, S549R, G1244E, G1349D, S1251N, and S1255P. It is estimated that the expansion to these mutations would make little difference to the numbers of patients eligible for treatment as these subgroups are very rare. Members noted that is common practice to do gene mapping in New Zealand.
- 6.16. The Committee noted there would be a significant financial impact to the Pharmaceutical Budget in listing ivacaftor at the current price. as treatment will be expected to be long term. Members noted that results from two new phase III trials (TRACTOR and TRANSPORT), studying ivacaftor in conjunction with Vertex's new product lumacaftor in patients homozygous for the F508del mutation, are expected later this year. Members noted that if the results of these two trials are positive there then would be a significant financial risk to the Pharmaceutical Budget. The F508del mutation is the most common mutation of the CFTR gene, opening treatment to ~75% of the CF population in New Zealand.
- 6.17. The Committee noted in the Medsafe datasheet for ivacaftor a requirement to reduce the dose of ivacaftor if co-administered with CYP3A inhibitors.
- 6.18. The Committee deferred making a recommendation on listing ivacaftor, pending further analysis by PHARMAC, clarification on which patient populations may benefit most and further information on the results of the trials with lumacaftor.

## 7. Adrenaline auto injectors application for funding for patients allergic to bee and wasp venom

### Application

- 7.1. The Committee reviewed an application from Allergy New Zealand for the listing of adrenaline auto injectors on the Pharmaceutical Schedule for the treatment of patients allergic to bee and wasp venom.

### Recommendation

- 7.2. The Committee **recommended** listing one adrenaline auto injector in a 12 month period for patients who have experienced an anaphylactic reaction to venom or food and who have been fully trained in the use of the auto injector and have an anaphylaxis action plan – with a medium priority similar to its previous recommendation.
- 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; and (vii) the direct cost to health service users.

### Discussion

- 7.4. The Committee noted that it had reviewed adrenaline auto injectors on three previous occasions and had previously recommended they be listed with a medium priority for adults and children at high risk of life threatening anaphylaxis to venom and food allergies. The Committee noted that the medium priority given at earlier meetings reflected the poor cost-effectiveness of this treatment. The Committee noted that the earlier assessments of adrenaline auto injectors for anaphylaxis due to food allergies and stings and the focus was generally on younger people whereas in Pumphrey et al (Clin Exp Allergy 2000;30:1144-1150) the average age of those dying with stings is 54 years.
- 7.5. The Committee noted that the current application has been narrowed to cover just those patients with a previous anaphylactic reaction to bee or wasp venom. The Committee noted that the applicant considered funding this group can be justified as anaphylaxis due to venom allergy is usually associated with hypotension and collapse, it often occurs in rural settings and can develop very quickly – symptoms can develop within five minutes and death within 15 minutes (before an ambulance could arrive). The Committee noted that the recommendation is that adrenaline generally needs to be administered within five minutes of a sting.
- 7.6. The Committee considered that it is difficult to justify funding treatment for bee and wasp allergies and not food and other allergies that may also result in severe, life threatening anaphylactic reactions. The Committee considered that in New Zealand many people are more than 15 minutes away from an ambulance and more people die from other causes of anaphylaxis than from venom.
- 7.7. The Committee noted that the applicant had suggested that the auto injectors be restricted to prescription by an immunologist or allergy specialist and that the patients should be considered for desensitisation by immunotherapy. The Committee noted that there are a limited number of allergy specialists in New Zealand and they tend to be located in the main centres. The Committee noted that immunotherapy requires oversight by an allergy specialist and requires a series of subcutaneous injections followed by monthly boosters for many years and the

recommendation is that the patient is professionally monitored for an hour after the injections.

- 7.8. The Committee noted that it is not possible to predict the outcome of the next sting – it could be more or less severe and immunotherapy is mostly used for those who had severe systemic reactions, reducing the risk and severity of future reactions. The Committee considered that predictors of severe systemic anaphylaxis to stings can include known allergy, older age, ACE inhibitors (and possibly other anti-hypertensives), tryptase concentrations, and one or more preceding stings with a less severe systemic reaction. The Committee noted that half of all fatal reactions occur without any prior reactions to stings.
- 7.9. The Committee noted that mortality from anaphylaxis is low at less than 1% of reactions. The Committee noted that Starship guidelines recommend auto injectors should be prescribed by Emergency Department physicians if someone has an anaphylactic reaction. The patient should be given instructions on use and referred to an allergy specialist. The Committee noted that adrenaline may need to be administered more than once during an anaphylactic reaction.
- 7.10. The Committee noted that the submission for funding was supported by a letter from the New Zealand Clinical Immunology and Allergy Group who consider that best practice is not followed in New Zealand and patients with anaphylaxis are often not referred to a specialist and are not offered immunotherapy.
- 7.11. The Committee considered the strength of the evidence supplied in the application to be weak and of poor quality, largely comprising expert opinion and guidelines; members however recognised that there is unlikely to ever be better evidence available as it would be unethical to conduct clinical trials in this area. The Committee considered that a syringe and ampoule may not be a suitable option for the community in an emergency situation, but recognised that patients may not use auto injectors when they are having an anaphylactic reaction for a number of reasons, including being afraid of the side effects, not realising that they are having an anaphylactic reaction, not having the auto injector with them.
- 7.12. The Committee noted that it is difficult to quantify the number of patients in New Zealand who have severe allergic reactions to stings as many are not recorded. The Committee noted the American Academy of Allergy, Asthma and Immunology 2009 estimate of 0.3 to 7.5% of people in the US and Europe with systemic allergic reactions to insect stings; the Immunology Allergy Clinic Nth America 2007 estimate that 3% of adults and 1% of children have systemic allergic reactions; Brown et al (Curr Opin Allergy Clin Immunol 2013) estimate of systemic reactions to honey bee stings at 0.5 to 2% of the population; and estimates by Smith et al of 45/100,000 annual incidence of anaphylactic reactions in adults in Auckland, of which approximately 30% are severe (unpublished data).
- 7.13. The Committee considered that desensitisation would not necessarily eliminate the need for auto injectors and patients would continue to need an auto injector after completion of a desensitisation course, but desensitisation would reduce the risk of the patient experiencing a severe reaction while still on maintenance. The Committee noted that approximately 50% of fatalities have had no previous history of allergy so such deaths would not be prevented, and that in the UK 9 out of 14 patients who had experienced previous severe systemic reactions and who had received adrenaline still died.

## 8. Multivitamin and mineral supplement for patients with burns

### Application

- 8.1. The Committee considered an application from the National Burns Centre for funding of a multivitamin and mineral preparation (Clinicians Multivitamin and Mineral Boost) for patients with burns and meet the criteria of the burns protocol.

### Recommendation

- 8.2. The Committee **recommended** that Clinicians Multivitamin and Mineral Boost be listed in Section H of Pharmaceutical Schedule (Hospital Pharmaceuticals - HML) for patients with burns with a medium priority subject to the following HML restrictions:

Restricted

*Limited to 3 months treatment*

Both:

1. Patient was admitted to hospital with burns; and
2. Any of the following:
  - 2.1 Burn size is greater than 15% of total body surface area (BSA) for all types of burns; or
  - 2.2 Burn size is greater than 10% of BSA for mid-dermal or deep dermal burns; or
  - 2.3 Nutritional status prior to admission or dietary intake is poor

- 8.3. The Committee **recommended** that Clinicians Multivitamin and Mineral Boost not be listed in Section B of the Pharmaceutical Schedule for community use.
- 8.4. 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 service.

### Discussion

- 8.5. The Committee considered an application for Clinicians Multivitamin and Mineral Boost capsules from a pharmacist on behalf of the National Burns Centre based at Middlemore Hospital.
- 8.6. The Committee noted patients with major burns have increased micronutrient requirements due to their hypermetabolic response, wound healing requirements and cutaneous exudative losses.
- 8.7. The Committee noted that previously children with burns received Penta-Vite multivitamin liquid but this was not included in the Hospital Medicines List. The Committee noted that adults received standard multivitamin preparations. The Committee noted the National Burns Centre has recently revised its guidelines which now recommend the Clinicians Multivitamin and Mineral Boost product for adults and children in addition to ascorbic acid, folic acid and zinc supplementation. Members noted that Clinicians Multivitamin and Mineral Boost is not listed on the Hospital Medicines List.
- 8.8. The Committee considered there appears to be little consistency internationally regarding the optimal regime for supplementation, however generally zinc, copper,

selenium and vitamin A, B, C E and folic acid seem to be recommended. Members noted there was no consensus on the appropriate dosage or route of delivery.

- 8.9. The Committee noted a number of vitamin and mineral preparations are already funded on the Pharmaceutical Schedule, however none contain all the components that are suggested to be important in supporting burn healing. The Committee noted there are no currently funded oral preparations that contain selenium or copper. The Committee considered a renal multivitamin product currently being developed would not be an appropriate alternative.
- 8.10. The Committee noted the Clinicians Multivitamin and Mineral Boost preparation is considered a dietary supplement and therefore current regulations regarding dietary supplements mean that it does not need to meet standards required for a registered medicine. Members noted the Clinicians brand is owned and manufactured by Douglas Pharmaceuticals.
- 8.11. The Committee considered the limited evidence for vitamin and mineral supplementation to support healing of burns to be of poor quality; however the general consensus of international experience and expert opinion suggests supplementation is of value. Members noted three review/guideline papers (Hall et al. *Nutrients* 2012;4:1154-65; Rousseau AF et al. *Clinical Nutrition* 2013;32(4):497-502; Nordlund MG et al. *J Burn Care Res* 2014;35(2):122-33) broadly support the utility of micronutrients in burn patients.
- 8.12. The Committee considered two papers (Berger et al, *Am J Clin Nutr* 2007;85:1293-300 & 1301-6) that examined the effect of supplementation with copper, selenium and zinc on various parameters of burn healing. The papers describe a small prospective, randomised, placebo-controlled trial in 21 adult patients with burns to greater than 20% of body surface area (45 +/- 21%). Members noted trace element supplementation was associated with early normalisation of the low plasma trace element concentrations usually observed in burned patients. This was associated with a significantly improved clinical course with lower grafting requirements and fewer pulmonary infections. There was also a trend toward shorter times of mechanical ventilation and length of intensive care stay but these results were not statistically significant. Safety of the regime was not specifically addressed but the authors note that the absence of any supernormal copper, selenium or zinc plasma concentrations and satisfactory clinical progress are arguments in favour of safety. Intravenous minerals (380 microgram selenium, 49 mg zinc and 3.7mg of copper) were given daily for 14 days if burns covered 20%-60% of BSA or 22 days if burns exceeded 60%. Members noted the small patient numbers and poor statistical design of this study.
- 8.13. The Committee noted the product proposed for listing is an oral preparation and oral absorption of many minerals is highly variable. Members noted the systemic effect of severe burns may also have an impact on bioavailability of micronutrients. The proposed formulation would only provide a small percentage of the doses used in the Berger et al papers (*Am J Clin Nutr* 2007;85:1293-300 & 1301-6).
- 8.14. The Committee noted the duration of supplementation in the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommended 7-8 days for burns to 20-40% BSA, 2 weeks for burns of 40-60% and 30 days for burns greater than 60% of total BSA. The Committee considered that these recommendations are relevant to the high level of intravenous supplementation given in the studies. Members considered there is less direct evidence for appropriate duration of lower dose oral supplementation.

- 8.15. The Committee noted there is no evidence for the particular product requested; however acknowledged the unmet clinical need and the lack of suitable alternatives currently available.
- 8.16. The Committee considered that community funding of the Clinicians Multivitamin and Mineral Boost would not be appropriate based on the evidence available and the likely duration of treatment. The Committee considered that continued use after discharge would not be necessary for most patients.
- 8.17. The Committee considered that there would be potential for significant financial risk if Clinicians Multivitamin and Mineral Boost capsules were listed with no restrictions as it may be used as a general multivitamin supplement. Members considered that should Clinicians Multivitamin and Mineral Boost product be listed in Section H that the financial impact would be low if appropriate restrictions were in place.
- 8.18. The Committee considered it would be appropriate to restrict use to burns patients who require hospital admission, are treated as per the national burns centre protocol and meet the criteria described in protocol. Members considered treatment should be limited to 3 months with no renewal.

## 9. Biosimilar Infliximab

### Application

- 9.1. The Committee reviewed an application from Hospira (New Zealand) Ltd for the listing of its biosimilar infliximab (CT-P13, Inflectra/Remsima) in Section H of the Pharmaceutical Schedule.

### Recommendation

- 9.2. The Committee **recommended** that subject to Medsafe approval, Hospira's biosimilar infliximab should be listed in Section H of the Pharmaceutical Schedule subject to the same restrictions as the Remicade (Janssen) brand of infliximab.
- 9.3. The Committee further **recommended** that PHARMAC run a Request for Proposals or Tender for the Sole Supply of infliximab for all indications currently funded.
- 9.4. 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 & disability support services; and (vi) the budgetary impact of any changes to the pharmaceutical schedule.

### Discussion

- 9.5. The Committee noted that infliximab is a chimeric monoclonal antibody that binds to soluble and transmembrane form of human tumour necrosis factor alpha (TNF $\alpha$ ), preventing cell activation, proliferation, cytokine production and other pro-inflammatory responses. Members noted that infliximab (Remicade, Janssen) is currently approved by Medsafe, and funded in DHB hospitals subject to restrictions, for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, psoriasis and ulcerative colitis. Members noted that infliximab is also funded in DHB hospitals subject to restrictions for off label use in Graft vs Host

Disease (GVHD) of the gut, severe, vision threatening ocular inflammation, severe uveitis and pulmonary sarcoidosis.

- 9.6. The Committee noted that prior to 1 July 2013 some DHBs were limiting access to infliximab due to its high cost and that since the Hospital Medicines List (HML) came into effect on 1 July 2013 the use of infliximab has increased significantly.
- 9.7. The Committee noted that Hospira's biosimilar infliximab (Inflectra/Remsuma) was not currently approved by Medsafe but that it was approved by the European Medicines Agency (EMA) and had been launched in some European countries and Medsafe is currently considering a submission. Members noted that in order to satisfy the EMA for approval a biosimilar must demonstrate that its variability in any parameter falls within the range of variability for the reference product and that any differences between it and the reference product have no clinically meaningful differences in quality, safety or efficacy. Members noted that the Committee for Medicinal Products for Human use (CHMP) noted that there were minor difference in Hospira's biosimilar infliximab and Remicade, however, they concluded that the quality of biosimilar infliximab was in line with the quality of other approved monoclonal antibodies. Further it stated that biosimilarity with the reference medicinal product (Remicade) has been demonstrated and the observed differences and the levels of these differences were acceptable.
- 9.8. The Committee considered evidence comparing Hospira's biosimilar infliximab with Remicade including evidence from two comparative clinical studies in patients with ankylosing spondylitis (AS) (Study CT-P13 1.1, PLANETAS, Park et al Ann Rheum Dis. 2013 ;72(10):1605-12) and rheumatoid arthritis (RA) (Study CT-P13 3.1, PLANETRA, Yoo et al Ann Rheum Dis. 2013;72(10):1613-20). Members noted that both PLANETAS and PLANETRA were randomised double blind studies and were conducted well. Members further noted that the trial designs were similar to the original Remicade trials conducted in these two conditions. The Committee considered that, based on the evidence it reviewed, Hospira's infliximab demonstrated same or similar quality, safety and efficacy to Remicade.
- 9.9. The Committee further considered that whilst there were no specific studies comparing Hospira's infliximab with Remicade in gastrointestinal, or other funded off-label indications there was no reason to consider that the two products would be any different in terms of quality, safety or efficacy in these settings. Members noted that inflammatory bowel diseases were naturally fluctuating conditions and Specialists were used to dealing with treatment failure and suboptimal treatment responses in these patients. Members considered that it would be difficult to distinguish a real difference in efficacy in patients treated with Remicade or Hospira's biosimilar infliximab from normal fluctuation as part of the natural disease course in these patients.
- 9.10. The Committee noted that there are several registry studies and two RCTs in progress, or planned, examining the use of Hospira's biosimilar infliximab in Inflammatory Bowel Disease (IBD). The Committee were also aware of a small study of 23 patients with IBD treated with Hospira's infliximab or Remicade which was not submitted with the application.
- 9.11. The Committee noted that like all biologics, biosimilar medicines have the potential to induce immune responses in patients. Members noted that the clinical consequence of immunogenicity, if present, was variable, in most cases no clinical consequence or some loss of efficacy. Members noted that infliximab (Remicade) is a particularly immunogenic molecule with antibody development apparent in 17-60% of patients treated (Purcell J, Investig Allergol Clin Immunol; 2008:18(5):335-42). Members considered that different immunogenicity of a biosimilar compared with its reference biologic resulting in significant differences in efficacy or safety

would be apparent in the phase 3 comparability clinical studies. Members considered that post marketing surveillance was important to rule out rare immunogenic consequences of biologics medicines, and this was no different for biosimilars compared with innovator biologics. Patients enrolled in the two RCTs PLANETAS and PLANETRA showed similar antibody response to Remicade and Hospira's infliximab and this was associated with loss of efficacy.

- 9.12. The Committee noted the caution from specialist societies in Europe and Canada about using biosimilar infliximab for Inflammatory Bowel Disease due to lack of direct comparisons with Remicade in this patient population. The Committee noted that process changes in the production of innovator products occur commonly resulting in variations between commercial lots (Schiestl et al Biotechnology Nature Biotechnology 2011, 29,310–312). Members considered that many of the commercially available innovator biologic molecules on the market were not exactly the same, but were comparable to, the originally produced batches of those products and therefore discounted the concerns about biosimilar infliximab. The Committee also noted that Gastroenterology Subcommittee would be meeting soon and requested the opinion of the Subcommittee on Hospira's biosimilar infliximab.
- 9.13. The Committee considered that it would be appropriate for PHARMAC to run a Sole Supply process for infliximab for all indications currently funded. Members further considered that it would be appropriate to award Hospira Sole Supply Status to Hospira's biosimilar infliximab if it was the preferred bid, subject to it gaining approval from MedSafe. Members considered that patients could be switched from Remicade to Hospira's biosimilar infliximab but recommended that PHARMAC provide educational material to prescribers and patients to support such a switch if implemented.
- 9.14. The Committee also considered the importance of pharmacovigilance and working with Medsafe and Hospira to implement such a programme should Hospira's biosimilar infliximab be funded. The Committee considered this an important aspect to reassure prescribers about the caution in proceeding with biosimilars specifically in Inflammatory Bowel Disease.

The minute of this item originally approved by PTAC was amended to correct a small number of factual matters at its November 2014 meeting. The version above is the corrected version.

## 10. **Phosphodiesterase V inhibitors (PDE5 inhibitors) and/or intracavernosal alprostadil for Erectile Dysfunction (ED) related to Spinal Cord Injury (SCI)**

### **Application**

- 10.1. PHARMAC has received an application from a clinician working at Burwood Spinal Unit, Canterbury District Health Board Spinal Unit for the listing of treatments in the HML and the Pharmaceutical Schedule for spinal cord injury-related erectile dysfunction.

### **Recommendation**

- 10.2. The Committee **recommended** that PHARMAC should attempt to engage with the Accident Compensation Corporation (ACC) to discuss the funding of phosphodiesterase V inhibitors (PDE5i) and/or intracavernosal alprostadil for Erectile Dysfunction (ED) in the hospital setting for spinal cord injury patients.
- 10.3. The Committee **recommended** that if ACC will fund these products in the hospitals setting for spinal cord injury patients, then there is no need for PHARMAC to amend Section H.

- 10.4. The Committee **recommended** that if ACC does not fund these products in the hospital setting, then access to PDE5 inhibitors and/or intracavernosal alprostadil should be widened in Section H with a medium priority.
- 10.5. The Decision Criteria particularly relevant to this recommendation are: (i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific peoples; (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,

## Discussion

- 10.6. The Committee noted that PHARMAC has received an application from a clinician working at Burwood Spinal Unit in the Canterbury District Health Board Spinal Unit for the listing of erectile dysfunction treatments in Section H for spinal cord injury (SCI) patients. Members noted that the treatments requested are phosphodiesterase V inhibitors (PDE5 inhibitors) and/or intracavernosal alprostadil.
- 10.7. The Committee noted that the clinician states that sexual dysfunction related to spinal injury needs to be dealt with on first admission. Members noted that the clinician also states that the issue is a high priority for spinal cord injury patients.
- 10.8. The Committee noted that erectile dysfunction (ED), the inability to achieve or maintain an erection sufficient for satisfactory sexual activity, is commonly a consequence of SCI with approximately 75% of men reporting this problem (Burns et al. Spine 2001;26:S129). Members noted that the extent of ED is affected by the type and level of SCI with greater recovery of sexual function observed in men with incomplete compared with complete lesions, upper compared with lower motor neuron lesions and higher compared with lower spinal cord injuries.
- 10.9. The Committee noted that the annual incidence of SCI in NZ is 30 per million and that Māori rates are higher at 46 per million and Pacific peoples rates higher still at 76 per million. In New Zealand, 80% of SCI occur in men and 80% are higher cord lesions (Derrett et al. Injury Prevention 2012;18:343–346).
- 10.10. Members considered that the annual incidence in the hospital setting would be less than 110 patients per year.
- 10.11. The Committee noted that the applicant states that men who have SCI are often in the prime of their life and have normal sexual function prior to their injury.
- 10.12. Members noted that the goal of treatment is satisfactory resumption of sexual relations. Members noted that there is debate regarding which end points are most clinically meaningful and indeed who should define these end points. The Committee noted that the most commonly employed method in recent studies is the 15 question International Index of Erectile Dysfunction Questionnaire (IIEF) (Rosen Int J Impot Res. 1999 Dec;11(6):319-26).
- 10.13. The Committee noted that the currently available treatment options include PDE5i, intracavernosal alprostadil, vacuum assistive devices and surgically implanted prostheses.
- 10.14. The Committee noted that all currently available PDE5 inhibitors result in similarly high rates of successful sexual intercourse (68-69% compared to 33-35% for placebo), and similar side effect profiles (Tsertsvadze et al. Ann Intern Med 2009;151:650). Members noted that in men with ED of all aetiologies, the three PDE5i's have similar rates of successful sexual intercourse; approximately double

the rate of placebo (Tsertvadze et al 2009). Members noted that tadalafil has a much longer half-life (17.5hr) compared to the other two medications, which have terminal half-lives of 4-5 hours.

- 10.15. The Committee noted that sildenafil is now off-patent and is significantly less expensive than the other two PDE5inhibitors. Members noted that the recommended dose for most men is 50 mg taken one hour before intercourse. Members noted that common adverse effects for all three PDE5i's include headache, flushing and dizziness.
- 10.16. The Committee noted that intracavernosal alprostadil is an intrapenile injection therapy of alprostadil, which is the generic name for prostaglandin E1. Members noted that an erection typically occurs within 5-20 minutes of administration and the dose is titrated to achieve an erection lasting <1 hour. Members noted that the main side-effects are priapism and pain at injection site.
- 10.17. Members noted that at the Burwood Spinal Unit, initiation and titration of ED treatments are offered at admission in their Sexuality and Intimacy Clinic.
- 10.18. The Committee noted PDE5 inhibitors are preferred by SCI patients over injectable alprostadil because of ease of their administration, and the risk of priapism and pain at injection site for men associated with alprostadil. Members noted that vacuum assistive devices require manual dexterity to put them on and surgical prostheses are invasive and carry higher risks of infection, mechanical failure and extrusion, especially among men with SCI (Biering-Sorensen et al. Spinal Cord 2001;39(9): 455).
- 10.19. The Committee noted a systematic review by Rizio et al (J Spinal Cord Med. 2012;35(4):219-28) which included studies of PDE5 inhibitors in SCI, which were ranked according to a scoring key developed to include studies examining efficacy and satisfaction rather than strength and quality of the evidence. The authors concluded that all three agents were comparably efficacious and satisfactory.
- 10.20. The Committee noted a study by Giulano et al (Annals of Neurology 1999;46:15-21). This was a randomised, multicentre double-blind, placebo-controlled, flexible dose, two-way crossover study assessing the efficacy and safety of sildenafil in men with ED caused by traumatic SCI. 178 men received placebo or sildenafil 1 hour before sexual activity for six weeks, followed by a two week washout period then the alternate treatment for six weeks. Members noted for all men (including those who reported no residual erectile function at baseline and those with complete spinal cord lesions), 76% reported improved erections compared to placebo and 80% improved sexual intercourse on the IIEF questionnaire (mean scores indicating "most times" vs "a few times" for both erections and sexual activity). Members noted that after six weeks, 58% of patients required the 100 mg sildenafil dose.
- 10.21. The Committee noted a study by Giuliano et al (Archives of Neurology 2007;64(11):1584-1592) who conducted a multicentre randomised double-blind placebo-controlled, flexible-dose parallel-group study in Europe. 142 patients took tadalafil and 44 took placebo for 12 weeks. Members noted that erections improved 84.6% vs 19.5% ( $p<0.001$ ) and ability to engage in sexual relations 78.5% vs 14.6% ( $p<0.001$ ).
- 10.22. The Committee noted a study by Del Popolo et al, (Spinal Cord 2004;42(11):644-8) who conducted a double-blinded cross-over study comparing sildenafil and tadalafil of four weeks duration for each drug separated by a 2 week wash-out period. Members noted that both drugs had similar efficacy, tadalafil was

preferred because patients were able to have an erection in the 24-36 hours after taking the medication.

- 10.23. The Committee noted the abstracts provided by the applicant describing fertility and sexual function concerns following SCI.
- 10.24. The Committee noted a case series by Tang et al (Paraplegia. 1995;33(12):731-3) which included 15 patients with SCI whose ED was treated with intracavernous alprostadil. 14 of 15 patients achieved an erection adequate for coitus and lasting at least 20 min. Pain at the injection site was the most common adverse reaction (2/15 patients).
- 10.25. The committee noted a review by DeForge et al (Spinal Cord 2006;44:465-73) which reviewed sexuality in persons with SCI and reported on the effectiveness of erectile interventions. The Committee noted that in this review, penile injections resulted in successful erectile function in 90% (95% CI 83%-97%) of men and sildenafil resulted in 79% (95% CI 68%-90%) success. Members noted that the authors comment on the lack of quality RCTs examining PDE5is in SCI patients and their inability to do a meta-analysis due to heterogeneity. Members noted that a meta-analysis of success rates of intracavernous injections included in this review included papaverine, phentolamine and combination medications not used in New Zealand. The Committee noted that studies related to vacuum tumescence devices and implanted prosthesis where >20yrs old, which may reflect that these have been relegated to third-line treatments.
- 10.26. Members considered that there are no access issues to erectile dysfunction treatments for spinal cord injury patients in the community setting as they are funded by the Accident Compensation Corporation (ACC).
- 10.27. The Committee considered that there would be a need for alprostadil if PDE5 inhibitors are contraindicated or not tolerated. Members noted that alprostadil requires training, up-titration and education, preferably in the context of a specialized sexuality/intimacy clinic.
- 10.28. Members considered the impact on the lives of SCI patients who respond to the medications and have improved erections and return of sexual activity; and their partners, and potentially their yet to be conceived children.
- 10.29. The Committee noted that there may be a health equity issue in providing funding to spinal cord injury patients only. Members considered that patients with other causes of erectile dysfunction, such as diabetes, hypertension, multiple sclerosis or damage after prostate surgery, could have a similar case for funding. The Committee noted that there was concern that any widening of access for these pharmaceuticals should be carefully considered, Members noted that amending on sildenafil had been discussed by the Tender Medical Subcommittee, but there were concerns of significant implications, both reputational and financially. The Committee noted there was potential for misuse of PDE5 inhibitors if they were listed in Section B of the Pharmaceutical Schedule for the treatment of erectile dysfunction.
- 10.30. The Committee considered that it would be appropriate for ACC to cover funding of these products in the hospital setting, given they provide funding in the community setting and that it falls within their remit. .

## 11. Gabapentin for uraemic pruritus

### Application

- 11.1. The Committee reviewed an application from a clinician for the funding of gabapentin for the treatment of uraemic pruritus

### Recommendation

- 11.2. The Committee **recommended** that gabapentin for uraemic pruritus be funded with a high priority, subject to the following restrictions:

**Initial application – (Chronic Kidney Disease- associated pruritus)** from any relevant practitioner. Approvals valid for 3 months for applications meeting the following criteria:

1. Treatment with a tricyclic antidepressant has been ineffective or not tolerated by the patient; and
2. The patient has Chronic Kidney Disease Stage 5 where no other cause for pruritus can be identified (e.g. scabies, allergy); and
3. The patient has persistent pruritus not relieved with a trial of emollient/moisturising creams alone

**Renewal- (Chronic Kidney Disease- associated pruritus)** from any relevant practitioner. Approvals valid for 2 years for applications meeting the following criteria:

1. The patient has demonstrated a significant improvement in itch.

Note: Dosage adjustment of gabapentin is recommended for patients with renal impairment. Gabapentin is not licensed for the treatment of chronic kidney- associated pruritus

- 11.3. The Decision Criteria particularly relevant to this recommendation are: (i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.

### Discussion

- 11.4. The Committee noted that gabapentin is a structural analogue of the neurotransmitter gamma-aminobutyric acid (GABA) and is indicated for the treatment of epilepsy and neuropathic pain.
- 11.5. The Committee noted that gabapentin is funded subject to Special Authority criteria for epilepsy and the treatment of neuropathic pain, where the patient has tried and failed, or has been unable to tolerate treatment with a tricyclic antidepressant.
- 11.6. The Committee noted an FDA (US Food and Drug Administration) warning about the increased risk of suicidal behaviour and ideation associated with gabapentin.
- 11.7. The Committee considered that internationally gabapentin is used for a variety of off-label indications.
- 11.8. The Committee considered that uraemic pruritus is better labelled Chronic Kidney Disease associated pruritus (CKD-associated pruritus).
- 11.9. The Committee noted that Pisoni et al. (Nephrol Dial Transplant 2006;21:3495-3505) reported pruritus to occur in approximately 36-50% of haemodialysis patients. The Committee considered that CKD-pruritus is not associated with

gender, age, ethnicity, duration of dialysis or cause of renal failure and that pruritus generally starts before dialysis commences. The Committee estimated that approximately one third of patients with Chronic Kidney Disease Stage 5 (CKD 5) who are approaching dialysis may develop pruritus. The Committee further estimated that 50% of these patients would require treatment (including those on dialysis).

- 11.10. The Committee considered that CKD-associated pruritus significantly affects quality of life and depression scores and that about 50% of patients are depressed.
- 11.11. The Committee considered the first step in treatment is optimising dialysis and attempting to reduce serum parathyroid hormone to normalise calcium / phosphorus. Members considered that non-soap cleansers and applying emollients can help to manage dry skin. The Committee noted the use of capsaicin cream is documented in the literature as a therapeutic option and considered that localised itch may be reduced by frequent applications of topical capsaicin, if tolerated. The Committee noted that capsaicin cream is only funded for patients who meet Special Authority criteria; which does not include CKD – associated pruritus as an indication. The Committee suggested PHARMAC investigate widening access to capsaicin cream for this indication.
- 11.12. Members considered UVB phototherapy, where available is the mainstay of treatment for severe CKD-associated pruritus. The Committee noted that Maori and Pacific people have a higher incidence of CKD and end stage renal failure. Members considered this population may be less likely to access phototherapy and may be less likely to respond due to their higher Fitzpatrick photo skin type.
- 11.13. The Committee noted that oral anti-histamines are frequently prescribed, but often have little benefit with the exception of tricyclic antidepressants that have additional anti-histamine effects (e.g. doxepin, amitriptyline). The Committee considered that a trial with a tricyclic antidepressant prior to initiation of gabapentin was appropriate and that it was likely in practice, for both agents to be trialled or used in combination should either agent prove ineffective.
- 11.14. The Committee considered other treatments reported in the literature to help some individuals including pregabalin, nalfurafine, activated charcoal, ondansetron, cholestyramine, naltrexone and thalidomide. The Committee noted that kidney transplantation remains the definitive therapy for CKD-associated pruritus.
- 11.15. The Committee considered the evidence provided by the applicant. Members considered the strength and quality of the evidence in support of gabapentin for CKD-associated pruritus to be moderate. The Committee noted two small randomized controlled trials demonstrated a positive effect of gabapentin 300mg after each haemodialysis session (or 400mg twice weekly), reporting clinically significant mean itch reduction versus placebo ( $p < 0.0001$ ). (Gunal AI et al. *Nephrol Dial Transplant* 2004;19:3137-9), (Naini AE et al. *Saudi J Kidney Dis Transpl* 2007;18:378-81). Members considered the available evidence demonstrated a favourable safety profile for this agent; however, gabapentin is primarily renally excreted so the half-life may be significantly prolonged in haemodialysis patients. The Committee considered that gabapentin has a narrow therapeutic window with risk of neurotoxicity for patients with renal impairment.
- 11.16. The Committee considered that CKD-associated pruritus may fall under the umbrella of neuropathic pain; however Members noted that the exact cause of CKD-associated pruritus is unknown and is likely to be due to be a combination of factors.

- 11.17. The Committee recommended that should access to gabapentin be widened the prescriber type should not be limited to ensure this did not create access issues, however the Committee recommended that a note should accompany the Special Authority regarding reduced dosing of gabapentin for patients with renal impairment.

## 12. Lidocaine 4% (LMX4) cream

### Application

- 12.1. The Committee reviewed an application from Orion Laboratories (NZ) Limited for the listing of lidocaine 4% cream (LMX4) on the Pharmaceutical Schedule for topical local anaesthesia.

### Recommendation

- 12.2. The Committee **recommended** that lidocaine 4% (LMX4) cream be listed in Section B of the Pharmaceutical Schedule subject to the same Special Authority restrictions as lidocaine 2.5% with prilocaine 2.5% cream (EMLA cream) provided it was no more expensive than EMLA cream.
- 12.3. The Committee **recommended** that lidocaine 4% (LMX4) cream be listed in Part II of Section H of the Pharmaceutical Schedule (the Hospital Medicines List; HML) without restrictions provided it was no more expensive than any other topical anaesthetic listed on the HML.
- 12.4. 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; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule, (vii) The direct cost to health service users.

### Discussion

- 12.5. The Committee noted that lidocaine 4% cream is a topical local anaesthetic cream containing lidocaine 4% in a liposome base and that the product was indicated for the topical anaesthesia of intact skin prior to superficial skin procedures, including insertion of intravenous (IV) catheters and blood sampling.
- 12.6. The Committee considered that topical anaesthetics are used for various cutaneous and mucous membrane conditions, including (but not limited to) pruritus and pain due to minor burns, skin eruptions (e.g., varicella, sunburn and insect bites), and local analgesia on intact skin prior to superficial skin procedures such as insertion of IV catheters and blood sampling. The Committee considered that the areas of use for topical anaesthetics are potentially wide-ranging and may also be used for wound dressing changes in patients with chronic wounds (e.g. to alleviate pain during debridement). Members considered that other potential uses could include cosmetic medical treatments and non-medical procedures such as electrolysis, intense pulsed light (IPL), tattoo removal and bikini waxing.
- 12.7. The Committee noted that lidocaine 2.5% with prilocaine 2.5% cream (EMLA cream), lidocaine 25 mcg with prilocaine 25 mcg patches (EMLA patches) and tetracaine (amethocaine) 4% gel (Ametop) were alternative topical anaesthetics available for use in hospitals.

- 12.8. The Committee noted that it was possible to use injected local anaesthetics in a similar setting to topical anaesthetics. However, the Committee noted that there was anxiety and pain associated with local anaesthetic injections.
- 12.9. The Committee noted that EMLA cream, is the alternative topical anaesthetic funded in community, although its funded use is restricted to children with a chronic medical condition requiring frequent injections or venepuncture.
- 12.10. The Committee considered that the evidence provided by the supplier in support of lidocaine 4% cream was of good quality and strength. The Committee considered the magnitude of the clinical effect for use in topical local anaesthesia to be moderate.
- 12.11. The Committee considered a systematic review of 25 randomised controlled trials including 2,096 participants, that compared the analgesic efficacy of various topical anaesthetics with infiltrated local anaesthesia (using injectable local anaesthetics) and compared the efficacy of each topically available amide or ester local anaesthetic with EMLA cream (Eidelman MD et al, Ann Emerg Med 2005; 46(4):343-351). The Committee noted there were inconsistent results in trials comparing the efficacy of EMLA cream with infiltrated local anaesthetic. Members considered that the results from the review suggested that tetracaine, liposome-encapsulated tetracaine and liposome-encapsulated lidocaine were at least as efficacious as EMLA cream.
- 12.12. The Committee considered the analgesic effect of lidocaine 4% cream to be similar to EMLA cream and tetracaine 4% gel. The Committee considered that lidocaine 4% cream had a faster onset of action (30 mins vs 60 mins) and a theoretical smaller risk of adverse effects compared to EMLA cream as it did not contain prilocaine. The Committee considered that there could be some practical benefit from a faster onset of action, although this would not provide any additional health benefits or risks. The Committee noted that the anaesthetic effect of lidocaine 4% cream typically lasts two to three hours however procedures were normally completed in 30 minutes.
- 12.13. The Committee considered that if lidocaine 4% cream was listed on the HML it would likely take a significant share of the topical anaesthetic market due to the faster onset of action.

### 13. Topical Anaesthetics

#### Application

- 13.1. The Committee reviewed a request from PHARMAC staff for advice on whether a wider range of topical anaesthetics should be funded on the Pharmaceutical Schedule.

#### Recommendations

- 13.2. The Committee deferred making a recommendation on the funding of lidocaine 4% with adrenaline 0.1% and tetracaine 0.5% solution (Topicaïne) for wound debridement pending a full review of the efficacy and safety for the product in the settings of repairing, cleaning or debriding wounds.
- 13.3. The Committee **recommended** that lidocaine 25 mcg with prilocaine 25 mcg patches (EMLA patches) not be listed in Section B of the Pharmaceutical Schedule, given the availability of EMLA cream and the financial risk associated with non-medical use.

- 13.4. The Committee **recommended** that the age restriction be removed from the Special Authority criteria for lidocaine 2.5% with prilocaine 2.5% cream (EMLA cream) in Section B of the Pharmaceutical Schedule, with a high priority.
- 13.5. The Committee **recommended** not to remove the Special Authority from EMLA cream in Section B of the Pharmaceutical Schedule while it remained at its current price, because of the financial risk associated with non-medical use.
- 13.6. The Committee **recommended** that tetracaine (amethocaine) 4% gel (Ametop) not be listed in Section B of the Pharmaceutical Schedule at the current price, given the availability of EMLA cream and the financial risk associated with open listing at the current price.

## **Discussion**

### **Lidocaine 4% with adrenaline 0.1% and tetracaine 0.5% solution (Topicaine)**

- 13.7. The Committee considered lidocaine 4% with adrenaline 0.1% and tetracaine 0.5% solution (Topicaine) would be used primarily for pain management when repairing or cleaning traumatic wounds but it may also be used for debridement of chronic wounds.
- 13.8. The Committee noted that Topicaine was listed in Part II of Section H of the Pharmaceutical Schedule (the Hospital Medicines List; HML) without restrictions. Members noted that other relevant local anaesthetics that are listed on the HML included lidocaine 2.5% with prilocaine 2.5% cream (EMLA), lidocaine 25 mcg with prilocaine 25 mcg patches (EMLA), tetracaine (amethocaine) 4% gel (Ametop), ethyl chloride spray, lidocaine 2% gel and lidocaine 2% with chlorhexidine 0.05% gel.
- 13.9. The Committee was not aware of widespread community use of Topicaine with the exception of afterhours clinics where patients were self-funding the product.
- 13.10. The Committee considered that Topicaine may reduce the need for an injection of local anaesthetic for some patients. The Committee noted that there are no funded treatment comparators for these indications in the community. The Committee considered the appropriate comparator for Topicaine and other topical anaesthetics under consideration for listing in Section B would most likely be lidocaine infiltration (using injectable lidocaine) and possibly methoxyflurane or nitrous oxide.
- 13.11. The Committee considered that there was insufficient evidence presented in the relevant treatment settings for it to make a funding recommendation for Topicaine.

### **Lidocaine 25 mcg with prilocaine 25 mcg patches (EMLA patches)**

- 13.12. The Committee noted the Analgesic Subcommittee of PTAC's advice for PHARMAC staff to investigate listing EMLA patches in community with no restrictions. The Committee considered that if EMLA patches were listed in community with no restrictions there would be a significant risk that the patches would be used for other indications (i.e. aside from a chronic medical condition requiring frequent injections or venepuncture), including vaccinations and molluscum contagiosum removal. Members considered that, although the patches were not as useful for non-medical use, for example electrolysis, tattoo removal and laser skin treatments, there would still be a significant financial risk from non-medical use if EMLA patches were listed in the community without restrictions.

13.13. The Committee noted that lidocaine 2.5% with prilocaine 2.5% cream (EMLA cream), is the alternative topical anaesthetic available in community. The Committee noted that it is funded in the community for children with a chronic medical condition requiring frequent injections or venepuncture. The Committee noted that it had previously endorsed the Analgesic Subcommittee's recommendation to remove the age restriction from the Special Authority criteria, and that it still supported this recommendation.

13.14. The Committee considered that a significant price reduction would be required to mitigate the risk associated with removing the access criteria to EMLA cream in the community.

#### **Tetracaine (amethocaine) 4% gel (Ametop)**

13.15. The Committee considered that topical anaesthetics are used for various cutaneous and mucous membrane conditions, including (but not limited to) pruritus and pain due to minor burns, skin eruptions (e.g., varicella, sunburn and insect bites), and local analgesia on intact skin prior to superficial skin procedures such as insertion of IV catheters and blood sampling. The Committee considered that the areas of use for topical anaesthetics are potentially wide-ranging and may also be used for wound dressing changes in patients with chronic wounds (e.g. to alleviate pain during debridement). Members considered that other potential uses could include cosmetic medical treatments and non-medical procedures such as electrolysis, intense pulsed light (IPL), tattoo removal and bikini waxing.

13.16. The Committee considered that listing tetracaine (amethocaine) 4% (Ametop) gel in the community with no restrictions and making it available on a Practitioners Supply Order (PSO) would have a high budget impact.

13.17. The Committee noted that, as with other topical anaesthetic gels and creams, the amount of tetracaine 4% gel used would depend on the size of the wound or the number of sites prepared for venepuncture.

13.18. The Committee noted that tetracaine 4% gel can be used without an occlusive dressing, although it is probably more effective with an occlusive dressing. The Committee noted that occlusive dressings are not supplied with the Ametop gel and considered that a sticking plaster or plastic wrap may provide adequate occlusion.

#### **Lidocaine 4% cream (LMX4)**

13.19. The Committee noted that it had separately reviewed a funding application to list lidocaine 4% cream (LMX4) on the Pharmaceutical Schedule, and had recommended that, subject to current access criteria, lidocaine 4% (LMX4) cream be listed in Section B and Section H of the Pharmaceutical Schedule provided it was no more expensive than currently listed topical local anaesthetics.

#### **Potential competitive process for topical anaesthetics**

13.20. The Committee considered that there would be some clinical benefit from listing a topical anaesthetic cream or gel without restrictions, in the setting of repairing, cleaning or debriding wounds; however, the Committee considered that the benefits were unlikely to outweigh the financial risks associated with open listing these products at their current prices.

13.21. As noted above, the Committee considered the appropriate comparator for topical anaesthetic creams and gels would be lidocaine infiltration (using injectable lidocaine) and possibly methoxyflurane or nitrous oxide. The Committee noted that lidocaine injection is available on a PSO however methoxyflurane or and nitrous oxide are not available funded in the community.

- 13.22. The Committee considered that it is possible and often appropriate to do these procedures without topical anaesthesia; non-medical interventions such as distraction techniques and positive suggestion may be alternatives to topical anaesthetics.
- 13.23. The Committee considered that it would be appropriate to run a competitive process in the community for one funded topical anaesthetic cream or gel. However, the Committee considered that this would not be appropriate for the hospital setting where it was important to have a range of treatment options.
- 13.24. The Committee considered that the following products would provide the same or similar therapeutic effect and could be included in a competitive process for funding in the community: lidocaine 4% cream, tetracaine (amethocaine) 4% gel and lidocaine 2.5% with prilocaine 2.5% cream.
- 13.25. The Committee considered that should a competitive process be run for sole supply of one topical anaesthetic in the community that a small 5 g tube would be the most useful presentation and that it would be reasonable to restrict funded access to use on a PSO, with a maximum of 5 tubes per PSO, providing that this did not restrict access to topical anaesthetics for the group of patients who currently access EMLA cream via Special Authority. The Committee considered that restricting community access to only a PSO, could mitigate the potential for extensive non-medical use, for example for hair removal, tattoos.
- 13.26. The Committee considered that if a competitive process was run for community supply, PHARMAC should ensure that any new product subsequently listed in Section B is also listed in Section H of the Pharmaceutical Schedule.
- 13.27. In the context of usage estimates, the Committee considered that patients would likely have at least two doses of topical anaesthetic cream applied at different sites due to the potential for not inserting the needle correctly the first time. This would mean that clinicians would likely use an entire 5 g tube per patient.
- 13.28. The Committee considered that the use of topical anaesthetics may improve adherence to medicines (or blood tests) administered via injections or venepuncture in a small minority of cases however other factors of the health care scenario (including relationships with practitioners) were likely to play a greater role.

## 14. Removal of Special Authorities

### Application

- 14.1. The Committee reviewed an application from PHARMAC regarding the removal of Special Authorities for a number of products currently listed on the Pharmaceutical Schedule.

#### 14.2. Perhexiline maleate

- 14.2.1. The Committee noted that there was evidence that perhexiline maleate would be effective in the treatment of venous leg ulcers, which was a currently unfunded indication. The Committee considered it was unlikely that there would be many other indications for use of perhexiline. The Committee noted that the drug was cheap and there would not be a fiscal risk in widening access.
- 14.2.2. The Committee **recommended** the removal of the Special Authority on perhexiline.

### 14.3. Midodrine

- 14.3.1. The Committee noted the risk of hypertension in elderly adults as a side effect of midodrine. The Committee noted that there were potential clinical risks to patients if midodrine was misprescribed. The Committee noted that midodrine was used infrequently for the treatment of Parkinson's and diabetes. The Committee considered that there was a low short-term financial risk. The Committee considered that there may be a long-term risk due to the potential for indication creep. The Committee noted that it was difficult to quantify the financial risk associated with open access.
- 14.3.2. The Committee **recommended** reducing the restrictions associated with midodrine but not open listing.
- 14.3.3. The Committee **recommended** removing the following restrictions from the Special Authority criteria:
  - 14.3.4. Patient has tried fludrocortisone (unless contra-indicated) with unsatisfactory results; and
  - 14.3.5. Patient has tried non pharmacological treatments such as support hose, increased salt intake, exercise, and elevation of head and trunk at night.

### 14.4. Nicorandil

- 14.4.1. The Committee considered that it was unlikely that there would be many other indications for nicorandil and there was a low fiscal risk of removing the Special Authority.
- 14.4.2. The Committee recommended the removal of the Special Authority on nicorandil.

### 14.5. Minoxidil

- 14.5.1. The Committee noted that minoxidil could be used for the treatment of hair loss; however oral minoxidil would result in hair growth over the entire body rather than the targeted approach with topical therapy. The Committee considered that there was a low fiscal risk of removing the Special Authority on minoxidil.
- 14.5.2. The Committee recommended the removal of the Special Authority on minoxidil.

### 14.6. Erythropoietin

- 14.6.1. The Committee noted the price decrease from the recent request for proposal. The Committee noted that erythropoietin was often requested for patients who refused blood transfusions, notably for religious reasons. The Committee noted the risk of stroke or myocardial infarction associated with erythropoietin. The Committee noted that there is potential for underestimation of the adverse reactions that may occur due to treatment with erythropoietin.
- 14.6.2. The Committee considered there would be a risk of inappropriate non-evidence based use if the drug was open listed. The Committee also considered that this risk would be hard to control if the Special Authority

was removed. The Committee noted the potential for non-therapeutic use by athletes as a performance-enhancer. The Committee noted the potential fiscal risk associated with inappropriate usage. The Committee noted that some prescribing risk was mitigated through regulation.

14.6.3. The Committee also noted that blood transfusions are expensive treatments and take up hospital day care capacity. It was also noted that blood transfusions also could be associated with adverse effects.

14.6.4. The Committee noted its previous recommendation to widen access to patients with myelodysplasia in both community and hospital settings and considered this remained appropriate.

14.6.5. The Committee **recommended** that PHARMAC staff present a paper dealing with the clinical effect and cost-effectiveness of removing the Special Authority.

#### 14.7. Imiquimod

14.7.1. The Committee noted that imiquimod was already less expensive than fluorouracil sodium cream. The Committee noted that imiquimod was currently less expensive than the alternative treatments and that removing the Special Authority would likely be cost saving.

14.7.2. The Committee **recommended** the removal of the Special Authority on imiquimod.

#### 14.8. Gabapentin

14.8.1. The Committee considered that there were multiple indications for the use of gabapentin. The Committee noted that gabapentin would be widely used if open listed. The Committee noted that the evidence for some indications was poor. The Committee noted that gabapentin may not be well tolerated and people would choose not to continue to use it. The Committee noted the potential for high growth due to indication creep. The Committee noted that open listing gabapentin was a financial risk.

14.8.2. The Committee noted that gabapentin may be given already as part of pain management. The Committee considered that pain relief options in the community were limited. The Committee noted that the main pain management options in the community included ibuprofen, tramadol and paracetamol.

14.8.3. The Committee **recommended** removing the Special Authority from gabapentin

#### 14.9. Mycophenolate mofetil

14.9.1. The Committee considered that the majority of indications for mycophenolate were already funded and there would be limited financial risk due to increased use. The Committee noted that mycophenolate may be used as an alternative first line agent to azathioprine.

14.9.2. The Committee **recommended** the removal of the Special Authority on mycophenolate.

14.10. **Bicalutamide**

14.10.1. The Committee considered that bicalutamide had only a few specialist indications and there would be limited financial risk due to increased use.

14.10.2. The Committee recommended the removal of the Special Authority on bicalutamide.

14.11. **Bee Venom allergy treatment and Wasp Venom allergy treatment**

14.11.1. The Committee noted that there was a low financial risk in removing the Special Authorities for bee and wasp venom allergy treatment.

14.11.2. The Committee recommended the removal of the Special Authority on bee and wasp venom treatment.

14.12. **Isotretinoin**

14.12.1. The Committee noted that a lower dose was potentially safer. The Committee noted that New Zealand was one of the only countries in the world without a central control of prescribing of isotretinoin. The Committee considered that in light of this the Special Authority was valuable tool to help ensure prescribers were up to date with prescribing of retinoids and to ensure appropriate prescribing for patients who could become pregnant.

14.12.2. The Committee **recommended** widening access to isotretinoin by removing the following Special Authority criterion requiring patients to have had an adequate trial of other treatments.

14.12.3. Patient has had an adequate trial on other available treatments and has received an inadequate response from these treatments or these are contraindicated; and

14.12.4. The Committee **recommended** amending the following criterion from the Special Authority:

Applicant has an up to date knowledge of the safety issues around isotretinoin and is competent to prescribe isotretinoin.

14.12.5. The Committee **recommended** removing all but the following Special Authority criteria (criterion 4.1) for renewal.

Patient is female and has been counselled and understands the risk of teratogenicity if isotretinoin is used during pregnancy and the applicant has ensured that the possibility of pregnancy has been excluded prior to the commencement of the treatment and that the patient is informed that she must not become pregnant during treatment and for a period of one month after the completion of the treatment; or

Patient is male.

14.13. **Acitretin**

14.13.1. The Committee considered the Special Authority to be valuable to help ensure prescribers were up to date with prescribing of retinoids and to ensure appropriate prescribing for patients who could become pregnant.

- 14.13.2. The Committee **recommended** amending the following criterion from the Special Authority:

Applicant has an up to date knowledge of the safety issues around acitretin and is competent to prescribe acitretin.

- 14.13.3. The Committee **recommended** removing the all but the following Special Authority criteria (criterion 3.1) for renewal.

Patient is female and has been counselled and understands the risk of teratogenicity if acitretin is used during pregnancy and the applicant has ensured that the possibility of pregnancy has been excluded prior to the commencement of the treatment and that the patient is informed that she must not become pregnant during treatment and for a period of two years after the completion of the treatment; or

Patient is male

## 15. **Ceftaroline fosamil for complicated Skin and Soft Tissue Infections (cSSTI) and Community- Acquired Pneumonia (CAP) in adults**

### **Application**

- 15.1. The Committee noted the application from AstraZeneca for the listing of ceftaroline fosamil in section H of the Pharmaceutical Schedule.

### **Recommendation**

- 15.2. The Committee **recommended** that ceftaroline fosamil be listed with a high priority in section H of the Pharmaceutical Schedule for multi-resistant organisms salvage therapy for patients where alternative therapies have failed or who have a contraindication or hypersensitivity to standard current therapies, and only on the recommendation of an Infectious Disease Physician or Clinical Microbiologist
- 15.3. The Decision Criteria particularly relevant to this recommendation are: (i) The health needs of all eligible people within New Zealand; (ii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iii) The clinical benefits and risks of pharmaceuticals; (iv) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; and (v) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.

### **Discussion**

- 15.4. The Committee noted that ceftaroline fosamil, the pro-drug of ceftaroline, is a new extended-spectrum cephalosporin that exhibits time-dependent bactericidal activity against numerous Gram-negative and Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *S. pneumoniae*. The Committee noted that, like other  $\beta$ -lactams, ceftaroline exerts its bactericidal effect by binding to key penicillin-binding proteins (PBPs). The Committee noted that ceftaroline has a high affinity for staphylococcal PBPs, and for MRSA PBP 2a.

- 15.5. The Committee noted that ceftaroline fosamil is indicated in adults for complicated skin and soft tissue infections and community-acquired pneumonia (CAP).
- 15.6. The Committee noted the minute of the Anti-Infective Subcommittee of PTAC, from its February 2014 meeting. The Committee noted that the Anti-Infective Subcommittee recommended declining the application for complicated skin and soft tissue infections as the current range of available therapies was effective for this indication. The Committee noted that the Anti-Infective Subcommittee considered that ceftaroline fosamil may have a place in CAP as salvage therapy but that it had no role as first-line therapy of CAP.
- 15.7. The Committee noted that the currently listed anti-MRSA antibiotics, daptomycin, linezolid, daptomycin and teicoplanin may be associated with non-susceptibility, adverse reactions and drug interactions. The Committee noted that there are toxicity issues with linezolid and resistance issues with vancomycin. The Committee consider that there was an unmet health need in patients where resistance or toxicity precludes the effective use of current agents. Members noted that ceftaroline has a different adverse effect profile to these agents.
- 15.8. The Committee considered that the evidence relating to clinical experience for the use of ceftaroline outside the approved indications is currently limited to observational.
- 15.9. The Committee noted a large retrospective evaluation of the effectiveness and safety of ceftaroline fosamil therapy which included off-label indications (Casapao et al, *Antimicrob Agents Chemother.* 2014; 58 (5):2541-6.) This review included 527 patients who received ceftaroline, 67% who were treated for off-label indications. Twenty-eight percent (148/527) of patients had bacteraemia. Most patients (80%) were initiated on ceftaroline after receipt of another antimicrobial, with 48% citing disease progression as a reason for switching. The median duration of ceftaroline treatment was 6 days, with an interquartile range of 4 to 9 days. A total of 327 (62%) patients were culture positive, and the most prevalent pathogen was *Staphylococcus aureus*, with a frequency of 83% (271/327). Of these patients, 88.9% (241/271) were infected with MRSA. Clinically, 88% (426/484) achieved clinical success and hospital mortality was seen in 8% (40/527).
- 15.10. The Committee considered that usage would be low as prescribing would be restricted by the requirement for the endorsement of an Infectious Disease Physician or Clinical Microbiologist which would ensure effective antimicrobial stewardship.
- 15.11. The Committee considered that ceftaroline fosamil should be listed in section H of the Pharmaceutical Schedule for multi-resistant organisms salvage therapy for patients where alternative therapies have failed or who have a contraindication or hypersensitivity to standard current therapies, and only on the recommendation of an Infectious Disease Physician or Clinical Microbiologist. The Committee however recommended changing the priority from medium to high.

## 16. Lixisenatide (Lyxumia) for the treatment of adults with Type II diabetes

### Application

16.1. The Committee noted the application from Sanofi for the listing of lixisenatide in the Pharmaceutical Schedule.

### Recommendation

16.2. The Committee **recommended** that lixisenatide be listed with a low priority in the Pharmaceutical Schedule for patients with Type II diabetes where alternative therapies have failed to achieve a target HbA1C or who have a contraindication or hypersensitivity to standard current therapies, prior to insulin

16.3. 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

16.4. The Committee noted that lixisenatide is a once daily injectable, selective glucagon-like peptide-1 (GLP-1) receptor agonist. Members noted that lixisenatide mimics GLP-1, stimulating glucose-dependent insulin release, as well as suppressing glucagon secretion and slowing gastric emptying. Members noted that lixisenatide is registered in New Zealand for the treatment of adults with type 2 diabetes to achieve glycaemic control in combination with metformin, metformin and sulphonylurea, basal insulin and sulphonylurea when these, together with diet and exercise, do not provide adequate glycaemic control.

16.5. The Committee noted the outstanding applications which had previously been reviewed by PTAC for products in the Glucagon-like peptide-1 (GLP-1), Sodium-Dependent Glucose Transporter Two (SGLT-2) and Dipeptidyl peptidase-4 (DPP4) categories. Members noted the December 2013 Diabetes Subcommittee relating to GLP-1s, SGLT-2s and DPP4s. The Committee noted the proposed Special Authority by the Diabetes Subcommittee and that the Diabetes Subcommittee would be meeting in August 2014 to determine an appropriate treatment regime for diabetes treatments including one or all of the new classes of agents.

16.6. The Committee noted the Diabetes Subcommittee recommendation that the products should not be funded if co-prescribed with insulin. The Committee considered that the reduction in HbA1C from insulin would be appropriate if HbA1C was not controlled by these therapies, including lixisenatide.

16.7. The Committee noted the evidence for lixisenatide came, the GetGoal series of clinical trials. The Committee considered that 6 key trials in this series were of good quality and reflected the populations for which the supplier was applying for funding (GetGoal.X,S,P, L. Dou 1 and L-Asia). The Committee noted that all studies were 24 weeks and the primary efficacy measure was absolute change in HbA1c from baseline to week 24. Secondary endpoints varied slightly, however all included the percentage of participants achieving HbA1c <7% or ≤6.5% at week 24,

changes in fasting plasma glucose (FPG) and body weight, from baseline to week 24.

16.8. The Committee noted that the reduction in HbA1C across the 5 placebo controlled trials were approximately 0.5% greater with lixisenatide compared to placebo. The Committee noted that the lixisenatide groups demonstrated a small mean weight decrease compared to the placebo group. The Committee considered that these reductions were similar to the results from the previously considered GLP-1 receptor agonists, exenatide and liraglutide.

16.9. Members noted that the major adverse event from treatment of lixisenatide was nausea. Members noted that Australian Pharmaceutical Benefits Scheme information which suggested an attrition rate with treatment with GLP1s with 34% of patients stopping after 6 months, rising to 50% at 12 months.

16.10. The Committee **recommended** that the Diabetes Subcommittee consider lixisenatide as part of its review of DDP4s, GLP1s, and SGLT2s at its August 2014 meeting.

16.11. The Committee considered that lixisenatide provided a similar efficacy to other GLP1s and recommended funding lixisenatide with a low priority as per the following Special Authority proposed by the Diabetes Subcommittee:

Initial application from any medical practitioner. Approvals valid for six months for applications meeting the following criteria:

1. Either:
  - 1.1. Patient is not achieving effective control of HbA1c despite treatment with maximum tolerated doses of metformin and sulphonylurea for at least 6 months; or
  - 1.2. Patient is not achieving target HbA1c despite treatment with maximum tolerated doses of sulphonylurea and metformin is contraindicated; or
  - 1.3. Patient is not achieving target HbA1c on maximum tolerated doses of metformin for the previous 6 months and is unable to use insulin or sulphonylurea as the risk of severe symptomatic hypoglycaemia is unacceptable in the opinion of the treating physician
2. Patient is not prescribed insulin
3. It is anticipated that a reduction in HbA1c of 5 mmol/mol would achieve the HbA1c target for that patient

Renewal from any medical practitioner. Approvals valid for two years for applications meeting the following criteria:

1. Patient has achieved an HbA1c reduction of at least 5 mmol/mol from baseline and;
2. Patient is not prescribed insulin

16.12. The Committee noted that the application was well presented, with key studies identified and provided in an easy to review format.

## 17. **STRIBILD (Co-formulated tenofovir/emtricitabine/elvitegravir/cobicistat) for the treatment of HIV-1**

### **Application**

17.1. PHARMAC have received an application from Gilead Sciences for the listing of Stribild in the Pharmaceutical Schedule for the treatment of HIV infection in treatment-naïve adults.

## Recommendation

- 17.2. The Committee **recommended** the listing of combination elvitegravir, cobicistat, tenofovir disoproxil fumarate and emtricitabine (Stribild) in the Pharmaceutical Schedule for the treatment of HIV infection only if cost-neutral for the life of the Stribild patent under the restrictions that apply to all antiretrovirals:
- 17.3. 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

- 17.4. The Committee noted that Stribild is indicated as a single tablet regimen for the treatment of HIV infection in treatment-naïve adults. Members noted that Stribild is a fixed dose combination of one integrase inhibitor (elvitegravir), one pharmacokinetic enhancer (cobicistat) and two nucleoside HIV-1 reverse transcriptase inhibitor (tenofovir disoproxil fumarate and emtricitabine).
- 17.5. The Committee noted that the pivotal evidence to support the efficacy of Stribild comes from the results of two similar double-blind, randomised, phase III studies.
- 17.6. The Committee noted a phase 3, non-inferiority study of treatment-naïve patients with a HIV-1 RNA concentration of 5000 copies per mL or more and susceptibility to atazanavir, emtricitabine, and tenofovir (DeJesus et al *Lancet*. 2012 Jun 30; 379(9835):2429-38). Members noted that patients were randomly assigned (1:1) to receive Stribild or atazanavir (ATV)/ritonavir (RTV) + emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) plus matching placebos, administered once daily. The primary endpoint was HIV RNA concentration of 50 copies per mL or less after 48 weeks, with a 12% non-inferiority margin. 1017 patients were screened, 715 were enrolled, and 708 were treated (353 with Stribild and 355 with ATV/RTV+FTC/TDF). Members noted that Stribild was non-inferior to ATV/RTV+FTC/TDF for the primary outcome (316 patients [89.5%] vs 308 patients [86.8%], adjusted difference 3.0%, 95% CI -1.9% to 7.8%). Members noted that both regimens had favourable safety and tolerability and that 13 (3.7%) versus 18 (5.1%) patients discontinued treatment because of adverse events.
- 17.7. The Committee noted the other phase 3 trial, where treatment-naïve patients with HIV RNA concentration of 5000 copies per mL or more, and susceptibility to efavirenz, emtricitabine, and tenofovir were randomly assigned to receive Stribild or Atripla (efavirenz/emtricitabine/tenofovir disoproxil fumarate), once daily, plus matching placebo (Sax et al (*Lancet*. 2012 Jun 30; 379(9835):2439-48). Members noted that the primary endpoint was HIV RNA concentration of fewer than 50 copies per mL at week 48. 700 patients were randomly assigned and treated (348 with Stribild, 352 with Atripla). The Committee noted that Stribild was non-inferior to Atripla and that 305/348 (87.6%) versus 296/352 (84.1%) of patients had HIV RNA concentrations of fewer than 50 copies per mL at week 48 (difference 3.6%, 95% CI -1.6% to 8.8%).
- 17.8. The Committee noted the updated data to 144 weeks from the two pivotal trials. The updated data from Sax et al (*Lancet*. 2012 Jun 30; 379(9835):2439-48) found that, at 144 weeks of treatment, 80 percent of Stribild patients (n=279/348) compared to 75 percent of patients receiving Atripla n=265/352) achieved HIV RNA

viral load of less than 50 copies/mL (95 percent CI for the difference: -1.3 to 11.1 percent for Stribild vs. Atripla). The Committee noted the updated data from DeJesus et al (Lancet. 2012 Jun 30; 379(9835):2429-38), 78 percent of Stribild patients (n=274/353) versus 75 percent of patients taking ATV/RTV+FTC/TDF (n=265/355) achieved HIV RNA less than 50 copies/mL (95 percent CI for the difference: -3.2 to 9.4 percent for Stribild vs. the atazanavir-based regimen). The Committee noted that for the updated data that there were no significant safety issues and resistance issues were as expected.

17.9. The Committee considered that the strength and quality of the evidence to be of very good strength and quality.

17.10. The Committee noted the results for Stribild was comparable to that achieved with raltegravir from the study that compared raltegravir versus efavirenz regimens in treatment-naive HIV-1-infected patients (Lennox et al J Acquir Immune Defic Syndr. 2010 Sep; 55(1):39-48). The Committee considered that the advantage of Stribild is associated with the single pill regimen. Members noted that the lower pill burden of Stribid compared with other once daily regimens was unlikely to have a significant impact on treatment adherence. The Committee considered that adherence and possibly virological suppression, was likely to be slightly better with once- vs twice-daily regimens. Members considered that there were adherence advantages for Stribild over twice daily raltegravir based regimes.