

PTAC meeting held on 7 & 8 May 2015

(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.

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1. Correspondence

Umeclidinium with vilanterol

- 1.1. The Committee noted correspondence from GlaxoSmithKline in response to the Committee's November 2014 meeting minutes on the treatment.
- 1.2. The Committee noted GlaxoSmithKline's comments in relation to concerns that the Committee had raised but considered that there was a lack of clinical study results on the effect Anoro Ellipta has on exacerbation and hospitalisation rates and a lack of comparative studies with the currently funded LAMAs and LABAs used together. Furthermore, the long term benefits of treatment with Anoro Ellipta remained unanswered.
- 1.3. The Committee noted that there were a number of new products that could potentially be funded for the treatment of COPD and recommended that the umeclidinium with vilanterol application be referred to the Respiratory Subcommittee for their clinical review and recommendations with respect to the role of this application, and other new applications, for new COPD-related products in relation to existing products.

2. Subcommittee Minutes

Cancer Treatments Subcommittee of PTAC (CaTSoP) Minutes, October 2014

- 2.1. The Committee noted the record of the CaTSoP meeting held on 3 October 2014.
- 2.2. The Committee accepted the recommendations in paragraphs 3.2, 4.2.3, 4.3.3, 4.8.4, 4.9.3, 4.9.4, 5.4, 5.7, 7.11 and 8.9.
- 2.3. Discussions in relation to the recommendation in 4.10.3 were deferred until the broader discussion of plerixafor later in the meeting.
- 2.4. The Committee noted the recommendation in paragraph 6.10 to fund dabrafenib for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma with low priority. However, the Committee reiterated its November 2014 **recommendation** that the application for dabrafenib for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma be declined.

Ophthalmology Subcommittee Minutes, October 2014

- 2.5. The Committee noted the record of the Ophthalmology Subcommittee meeting held on 30 October 2014.
- 2.6. The Committee noted it had previously reviewed the Ophthalmology Subcommittee minute relating to aflibercept at its February 2015 meeting in conjunction with a funding application. The Committee noted its recommendation that PHARMAC run a Request for Proposals for second line anti-vascular endothelial growth factor (anti-VEGF) treatment of wet Aged-related Macular Degeneration following bevacizumab treatment.
- 2.7. The Committee noted it had previously accepted the minute of the Ophthalmology Subcommittee relating to biosimilar infliximab.
- 2.8. The Committee accepted the remainder of the minutes.

Nephrology Subcommittee Minutes, December 2014

- 2.9. The Committee noted the record of the Nephrology Subcommittee meeting held on 2 December 2014.

- 2.10. The Committee noted that the term “unresponsive” in paragraph 4.13 relating to the recommended amendments to Special Authority for candesartan needed be further defined. The Committee considered there would be some fiscal risk if access was widened at the current price, however this may not be the case if the price of candesartan is reduced as a result of a future tender decision.
- 2.11. The Committee noted the Nephrology Subcommittee’s recommendation in paragraph 4.19 in relation to potassium citrate; however, the Committee considered it should review a funding application for this product at a future PTAC meeting once a registered product is available.
- 2.12. The Committee noted the Nephrology Subcommittee’s recommendation in paragraph 6.2 in relation to rituximab in nephrotic syndrome; however, the Committee considered it should review this application at a future PTAC meeting.
- 2.13. The Committee noted that they had already reviewed cinacalcet at their February 2015 meeting and had recommended that it be declined.
- 2.14. The Committee noted and accepted the Special Authority criteria proposed in paragraph 11.2 for rituximab in ANCA-associated vasculitis.
- 2.15. The Committee accepted the remainder of the minutes.

Immunisation Subcommittee Minutes, February 2015

- 2.16. The Committee noted the record of the Immunisation Subcommittee meeting on 18 February 2015.
- 2.17. The Committee accepted the recommendations in paragraphs 3.5, 3.8, 5.10, 5.15, 5.16, 5.23, 5.26, 6.7, 6.8, 6.12, 8.11, 9.6.
- 2.18. In relation to 7.12, the Committee requested that the CUA analysis be brought to PTAC for review along with analysis of the costs associated with a catch-up program and information on the new zoster vaccine recently published in the NEJM.

Anti-Infective Subcommittee Minutes, December 2014

- 2.19. The Committee noted the record of the Anti-Infective Subcommittee meeting on 1 December 2014.
- 2.20. The Committee accepted the recommendations in paragraphs 3.12, 3.23, 3.30, 3.35, 3.39, 3.42, 3.43, 4.10, 4.11, 4.12, 5.6, 7.6, 8.6 and 9.7.
- 2.21. The Committee noted the Anti-Infective Subcommittee’s recommendation in paragraph 3.51 in relation to tobramycin for non-cystic fibrosis bronchiectasis; however, the Committee considered it should review this application at a future PTAC meeting.
- 2.22. The Committee noted that the recommendations made by the Anti-Infective Subcommittee in paragraphs 6.17 and 6.18 in relation to sofosbuvir differed from those made by the Committee at its August 2014 meeting. The Committee accepted the recommendations made by the Subcommittee and acknowledged that these would now become the recommendations of the Committee.

3. Sofosbuvir with ledipasvir for hepatitis C

Application

- 3.1. The Committee considered an application from Gilead Sciences for the funding of ledipasvir/sofosbuvir (Harvoni) for the treatment of chronic hepatitis C virus (HCV) infection in adults.

Recommendation

- 3.2. The Committee **recommended** that ledipasvir with sofosbuvir should be funded with a high priority for the following subpopulations:
- HCV patients with decompensated cirrhosis (all genotypes)
 - HCV patients pre/post liver transplant (all genotypes)
 - HCV patients with essential mixed cryoglobulinaemia (with associated purpuric skin rash, cryoglobulinaemic glomerulonephritis and systemic vasculitis).
- 3.3. The Committee **recommended** that ledipasvir with sofosbuvir should be funded for all other subpopulations of patients with chronic hepatitis C with a low priority based solely on fiscal risk.
- 3.4. 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; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 3.5. The Committee noted that the options for chronic hepatitis C treatment have developed quickly in recent years and advice relating to this area is rapidly evolving. The Committee noted that since PTAC last reviewed the literature relating to chronic hepatitis C during its deliberations on sofosbuvir (used in conjunction with peg-interferon and ribavirin) in August 2014, further trials have been published on multiple treatment regimens.
- 3.6. The Committee noted that the funded treatment, boceprevir is now no longer recommended in a number of international guidelines. It noted the Canadian Association for the Liver 2015 Consensus Guidelines that suggest that first generation protein inhibitors should no longer be used except in rare circumstances where treatment is urgent and access to newer agents is not available.
- 3.7. The Committee noted the number of New Zealand patients accessing currently funded treatments is declining with less than half the number of patients treated in 2014 via the pharmaceutical schedule compared with the more than 700 patients treated in 2010. The Committee considered that contributing factors to this reduction may be due to the suggestion that boceprevir may be more toxic than indicated in clinical trials, that some patients are currently able to access clinical trials for novel chronic hepatitis C treatment and that the majority of patients who could wait were postponing treatment in the hope that access to novel agents will be available in a short timeframe.
- 3.8. The Committee considered that there is currently no funded treatment available, and therefore unmet need, for patients with chronic hepatitis C in the following subgroups; patients who require treatment following the failure of boceprevir based triple therapy (boceprevir/ pegylated interferon/ ribavirin), patients with hepatitis C virus genotype 1 who are non-responders to pegylated interferon/ ribavirin therapy who received treatment after 2004, patients with hepatitis C virus genotype 2, 3, 4, 5 or 6 in whom initial treatment with pegylated interferon/ ribavirin fails, patients with HIV co-infection in whom initial treatment with pegylated interferon/ ribavirin fails and patients who are ineligible, or unable to tolerate treatment with boceprevir/ pegylated interferon/ ribavirin therapy.

- 3.9. The Committee noted that ledipasvir/sofosbuvir is used as an interferon free regimen. The Committee noted that interferon based regimens are contraindicated in those patients with decompensated liver disease.

Efficacy of ledipasvir/sofosbuvir

- 3.10. Members considered that the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines, Recommendations on Treatment of Hepatitis C 2015 (EASL, 2015, Journal of Hepatology – accepted for publication on 25 March 2015) provided an excellent summary of current evidence relating to the treatment of chronic hepatitis C.
- 3.11. The Committee reviewed the evidence presented for ledipasvir/sofosbuvir. The Committee considered that the evidence for ledipasvir/sofosbuvir is strong and of very high quality for hepatitis C virus genotype 1. However, the Committee considered that there is a lack of mature data on the use of the ledipasvir component of this pharmaceutical in hepatitis C virus genotypes 2 and 3, although preliminary data shows good efficacy. The Committee noted that in New Zealand, patients with hepatitis C virus genotype 3 make up approximately 35% of the chronic hepatitis C population. The Committee noted that the EASL Clinical Practice Guidelines, Recommendations on Treatment of Hepatitis C 2015 currently do not recommend the use of ledipasvir/sofosbuvir in patients with hepatitis C virus genotype 2 and 3.
- 3.12. The Committee noted that ledipasvir/sofosbuvir demonstrates a >90% sustained virologic response 12 weeks after cessation of treatment (SVR12) across genotypes, across different disease states, independent of prior treatment. Genotype 1 SVR12 rates often exceed 95%. Ledipasvir/sofosbuvir was combined with ribavirin in some indications. These SVR12 rates were markedly superior to rates achieved with the currently funded therapies. Members noted long-term follow-up studies showing SVR12 was associated with a virological cure in over 99% of cases, and that this view was supported by EASL. The Committee considered that newer treatments had markedly improved efficacy and tolerability and reduced treatment duration over currently funded chronic hepatitis C treatments.
- 3.13. The Committee discussed the adverse effects of ledipasvir with sofosbuvir. The Committee noted that no dose adjustment is recommended for patients with mild, moderate or severe renal or hepatic impairment, The Committee noted that neither sofosbuvir, ledipasvir nor GS-331007 (a product of sofosbuvir) inhibit or induce CYP or UGT1A1 enzymes. The Committee noted that concurrent rifampicin treatment may have an effect on the levels of ledipasvir/sofosbuvir leading to a reduced therapeutic effect of ledipasvir/sofosbuvir, although the likelihood of a patient requiring concomitant therapy was very low. The Committee considered that generally ledipasvir/sofosbuvir is well tolerated. It considered that the discontinuation rates in trials were around 0-2% which it considered to be low. Members noted that in some trials, ledipasvir/sofosbuvir was used in combination with ribavirin. Members noted the safety profile of ribavirin.
- 3.14. The Committee discussed the issue of compliance. Members considered that compliance would have a large effect on the efficacy of treatment. However members noted the regimen was generally one pill once a day.
- 3.15. Members discussed the potential for reinfection with hepatitis C due to recurrent or persistent risk behaviour. The Committee considered that the numbers of patients who are at risk of reinfection due to persistent or recurrent risk behaviour are likely to be low with risk behaviour having been historical in nature for many. The Committee considered that reported rates of reinfections following successful treatment for chronic hepatitis C among patients who are at high risk of reinfection are low, with estimates of between 1-5% re-infected per year. However, the Committee discussed whether the availability and ease of interferon free therapy may impact and increase the likelihood of reinfection for high risk patients. Members considered that data had not been presented that could address this question.

Subgroups

- 3.16. The Committee noted that the supplier's submission proposed funding for all chronic hepatitis C patients in New Zealand. Members considered that the pricing proposed in the application would have a very significant fiscal impact and that the supplier had made no attempt to address this fiscal risk.
- 3.17. Members considered that the patient numbers indicated by the supplier in the application could be a significant underestimate due to increased efforts to diagnose hepatitis C virus infection in New Zealand, the decline in use of current therapy, the current number of patients enrolled in clinical trials and the desire by both patients and clinicians to use non-interferon regimens. Members considered that the true cost of the proposal may be even higher than described in the application.
- 3.18. The Committee noted the EASL Clinical Practice Guidelines, Recommendations on Treatment of Hepatitis C 2015 which considered that not every chronic hepatitis C patient will be able to be treated in the next few years due to financial consideration and therefore prioritisation is necessary. Members considered that due to the potential budget impact of ledipasvir/sofosbuvir, prioritisation of different subgroups of chronic hepatitis C patients may be appropriate. Members considered a mechanism to allow appropriate targeted access to these treatments may be through the use of restrictions such as Special Authority criteria.
- 3.19. Members considered it relevant to give higher priority to patients whose urgency for treatment is higher. Members noted evidence for use of ledipasvir/sofosbuvir for patients with decompensated cirrhosis (ELECTRON-2 study, Gane, 2014. SOLAR-1 study, Reddy, 2014. SOLAR-2, Manns, 2015) which indicated that SVR12 rates of 89% were achievable when used in combination with ribavirin. Members noted the effect of clearing the viral load on the liver included improvements in Model for End-Stage Liver Disease (MELD) and Child-Pugh scores.
- 3.20. Members noted evidence for the use of ledipasvir/sofosbuvir for patients post liver transplantation (SOLAR-1 study, Reddy, 2014. SOLAR-2, Manns, 2015 EASL Clinical Practice Guidelines, Recommendations on Treatment of Hepatitis C 2015 Journal of Hepatology). Members considered that in patients who have chronic hepatitis C and receive a liver transplant, recurrence of hepatitis C virus in the graft is universal and that this would reduce the life of the graft. The Committee considered that successful treatment of chronic hepatitis C prior to transplant would achieve two goals; it would prevent recurrence of infection post-transplant, and would also improve the function of the liver before transplant in those patients with decompensated liver disease. Members considered that prevention of graft infection substantially facilitates post-transplant management. Members noted that patients commenced treatment up to 48 weeks prior to their transplantation (EASL Clinical Practice Guidelines, Recommendations on Treatment of Hepatitis C 2015 Journal of Hepatology).
- 3.21. Members noted the advice from the Anti-Infective Subcommittee of PTAC from its December 2014 meeting in relation to the identification of hepatitis C infected subpopulations that were a high priority for sofosbuvir compared to currently available treatments. The Committee considered that it was appropriate that the same subpopulations should be identified as a high priority for ledipasvir/sofosbuvir compared to currently available treatments.
- 3.22. Members also discussed the issues relating to delaying curative treatment at different stages of disease progression. They considered that, even if an SVR12 is achieved, those patients that had already progressed to cirrhosis would be at increased risk of potential life-threatening complications including hepatocellular carcinoma and oesophageal varices. The Committee considered that these patients would likely require indefinite follow-up involving surveillance for these complications. The Committee considered that should an SVR12 be achieved prior to progression to cirrhosis, it is likely that a patient will be able to be discharged from ongoing follow up. Some members

considered that while those who are in more advanced stages of disease are at greater risk, earlier treatment could provide the greatest gains. Other members noted that, due to the slow progression of disease, early treatment may mean treating a patient who would not have experienced a significant health loss.

- 3.23. Members considered that, were ledipasvir/sofosbuvir to be funded prior to the development of decompensated cirrhosis, this may move some patients with chronic hepatitis C from being treated in a hospital setting, to be treated in a community setting.
- 3.24. Members considered that there are benefits to ledipasvir/sofosbuvir which are not found with sofosbuvir treatment used with pegylated interferon and ribavirin, including increased SVR rates, increased tolerability and reduced duration of treatment.
- 3.25. Members again noted the rapidly changing landscape associated with novel treatments for chronic hepatitis C and that a number of alternative treatments are in development which may provide further benefits such as reduced treatment durations and further reductions in the price. The Committee discussed whether the novel treatments presented an opportunity to eradicate hepatitis C. Members considered that at current prices, this opportunity is not an option. The Committee considered that there is an opportunity for all interested stakeholders to work together to achieve this objective.

4. Ustekinumab for severe chronic plaque psoriasis

Application

- 4.1. The Committee considered an application from a clinician on behalf of the New Zealand Dermatological Society to list ustekinumab (Stelara) on the Pharmaceutical Schedule for the treatment of severe chronic plaque psoriasis.

Recommendation

- 4.1. The Committee **recommended** that ustekinumab be funded only if cost neutral to adalimumab.
- 4.2. *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

- 4.3. The Committee noted that PTAC reviewed an application from Janssen-Cilag to fund ustekinumab in May 2011 for the treatment of severe chronic plaque psoriasis. The Committee noted that, at that time, it had recommended that ustekinumab be listed only if cost neutral to other funded biologics, that the 90 mg dose be considered for funding only if cost neutral to the 45 mg dose, and that a limit of two biologic therapies be included as part of the Special Authority.
- 4.4. The Committee noted that the current application had been submitted on behalf of the New Zealand Dermatology Society. Members noted a similar listing was reviewed by PTAC previously been considered with the Janssen-Cilag application in 2011.
- 4.5. The Committee noted that most of the evidence supplied by the applicant had already been reviewed by the Committee in May 2011. This included three key clinical trials, the PHOENIX I, PHOENIX II and ACCEPT trials. The application however also included new evidence, including a study by Papp et al 2013 (Br J Dermatol 2013;168(4):844-854) examining the long-term safety of ustekinumab, and two meta-analyses (Lin et al 2012. Arch Dermatol. 2012;148(12):1403-1410; Schmitt et al 2014. Br J Dermatol. 2014; 170(2):274-304) comparing ustekinumab with other systemic treatments.

- 4.6. The Committee considered psoriasis is a significant health concern in New Zealand. Members noted estimates of 76,000 to 114,000 patients in New Zealand with chronic plaque psoriasis, of whom perhaps 380-570 do not respond adequately to non-biologic systemic treatments.
- 4.7. The Committee considered that there is significant morbidity associated with psoriasis, and patients experience varying levels of physical discomfort and disability.
- 4.8. The Committee noted that ustekinumab, a monoclonal antibody, has a different mode of action from other biologics (adalimumab, etanercept, and infliximab) listed on the Pharmaceutical Schedule for the treatment of psoriasis. Ustekinumab binds to the shared p40 protein subunit of IL-12 and IL-23, which prevents T-cell activation.
- 4.9. The Committee noted the PHONEIX I trial (Leonardi et al. Lancet 2008; 371(9625):1665-74), a randomised, parallel, double-blind, placebo-controlled study. The study enrolled 766 patients with moderate-severe plaque psoriasis, 50% of whom had previously been treated with a biological agent and discontinued treatment at least 3 months prior to randomisation. Patients were randomised to subcutaneous injections of ustekinumab 45mg (n=255); ustekinumab 90 mg (n=256); or placebo (n=255). Patients were treated over three phases, with patients being evaluated at the placebo-controlled phase (weeks 0-12), a placebo-crossover and active treatment phase (weeks 12-40), and a randomised withdrawal phase (weeks 40-76). The Committee noted that a significantly higher proportion of patients reached the primary endpoint (A 75% reduction in baseline PASI (Psoriasis Area and Severity Index) score) by week 12 in both the ustekinumab 45 mg (67.1%) and 90 mg (66.4%) groups when compared to placebo (3.1%) (P<0.0001). The Committee noted that a maximum response was demonstrated by 20 weeks in 74.9% of the ustekinumab 45mg group and 83.5% of the 90mg group, with response rates generally maintained through to week 40 when re-randomisation occurred. The Committee also noted that incidences and types of adverse events were generally comparable with placebo during the study; however, the study was underpowered to detect significant differences in rare serious long-term adverse events.
- 4.10. The Committee noted the PHONEIX II trial (Papp et al. Lancet 2008;371(9625):1675-1684), a phase III, multicentre, randomised, double-blind, placebo controlled study. The study enrolled 1230 patients with moderate-severe plaque psoriasis, who were randomly and evenly assigned to ustekinumab 45mg, 90 mg, and placebo groups. At week 28, partial responders (patients achieving ≥50% but <75% improvement from baseline in PASI) were re-randomised to continue dosing every 12 weeks or escalate to dosing every 8 weeks. The primary endpoint (PASI 75) was achieved in 66.7% of patients receiving ustekinumab 45mg and 75.7% receiving ustekinumab 90mg. The Committee noted secondary outcomes, Physicians' Global Assessment score of 0 or 1, and median changes in DLQI scores, significantly favored the ustekinumab groups at week 12. Partial responders receiving ustekinumab 90 mg with dosing intensification achieved a greater PASI 75 response rate at 68.8% (patients dosing every 8 weeks) vs 33.3% (patients dosing every 12 weeks). However, partial responders at week 28 were more likely to have been treated previously with a biologic (21.5% vs 12.1%, p=0.024) than responders, and partial responders also were more likely than responders to have failed treatment with at least one conventional systemic or biological agent. Members noted that ustekinumab was generally well tolerated at both doses and dosing schedules. By 52 weeks, the incidences of adverse events, serious adverse events, or adverse events leading to treatment discontinuation reported in the treatment groups were similar to the placebo group.
- 4.11. The Committee noted the ACCEPT trial (Griffiths et al. N Eng J Med. 2010;362(2)), a multicentre, randomised active-controlled study directly comparing both doses of ustekinumab (45 mg and 90 mg) with high dose etanercept (50 mg twice weekly). The Committee noted the trial enrolled patients who had chronic plaque psoriasis, with only 10% of the patients having previously used biologics. The Committee noted the primary endpoint PASI 75 at week 12 was achieved by 67.5%, 73.8% ,and 56.8% of patients in the ustekinumab 45 mg and 90 mg groups and the high dose etanercept group

respectively. The Committee noted the secondary endpoint, the Physicians Global Assessment score of 0 or 1 was achieved by 65.1%, 70.6% and 49% of 45 mg, 90 mg ustekinumab groups and the etanercept group, respectively. It was also noted by the Committee that of the patients in the trial who did not respond to etanercept, 48.9% achieved PASI 75, and 23.4% achieved PASI 90 within 12 weeks after the crossover to 90mg ustekinumab, and 40.4% achieved the secondary endpoint (Physicians Global Assessment scores of 0 or 1) after cross over. Members noted that no significant safety signals emerged from this trial, and that safety patterns of adverse events and serious adverse events were similar across all dose groups, and were also similar before and after crossover from etanercept to ustekinumab.

- 4.12. The Committee considered a Bayesian network meta-analysis indirectly comparing the efficacy of ustekinumab against other biologic agents using the PASI measure in adult patients with moderate-severe plaque psoriasis (Lin et al. Arch Dermatol.(2012;148(12):1403-1410). The Committee noted the study incorporated 17 high quality RCTs into the Bayesian network meta-analysis. All trials had placebo as a comparator, except for one that had etanercept as the comparator, and all had PASI 75 at 10-16 weeks as the primary endpoint. Patient characteristics, duration and severity of disease were similar across trials. Members also noted that in pair-wise comparisons, ustekinumab was reported more likely to achieve a PASI 75 only against adalimumab (OR 1.84 CI 1.01-3.54), and etanercept (OR 2.07, CI 1.42-3.06), but was inferior when compared to infliximab (OR 0.36 CI 0.14-0.82).
- 4.13. The Committee noted that there have been no new head-to-head trials since PTAC last reviewed this agent, and the new evidence was limited to indirect comparisons through meta-analyses.
- 4.14. The Committee considered a meta-analysis of RCTs that evaluated the efficacy of systemic treatments for moderate-severe plaque psoriasis (Schmitt et al. Br J Dermatol. 2014;170(2):274–304). The Committee noted that out of the systemic treatment trials identified in the meta-analysis, five trials were of ustekinumab, with seven infliximab trials and 14 etanercept trials. The Committee noted that the meta-analysis reported infliximab the most efficacious at achieving PASI 75 in 10-16 weeks (absolute risk difference 76%, CI 73-79%). Adalimumab and ustekinumab at both doses had reportedly similar efficacy (RD 61-69%) and etanercept at once weekly dosing had the lowest efficacy (RD 31%).
- 4.15. The Committee noted a recent study by Papp et al. (Br J Dermat 2013;168(4):844-854) reported long term safety outcomes of ustekinumab after 5 years of treatment by pooling four studies of ustekinumab for psoriasis. The study reported no emerging safety issues (specifically serious infections, malignancies or major cardiovascular events) from ustekinumab use compared with other biologic treatments. The Committee noted that previously safety data had been limited to 18 months. The Committee considered that although this study did offer further clarity on long-term safety, it was a non-comparative study, and future pharmacovigilance is important. The Committee noted the meta-analyses by Lin et al 2012 and Schmitt et al 2014 suggested infliximab was similar if not more efficacious than ustekinumab in treating moderate-severe plaque psoriasis, however it was noted that there was a relative lack of access to day care infusion facilities which maybe a limiting factor in access to infliximab. .
- 4.16. The Committee considered that current evidence indicates ustekinumab is likely to be more effective than etanercept in the treatment of severe chronic plaque psoriasis but has similar efficacy to adalimumab and infliximab. The Committee noted that infliximab is not currently widely used for psoriasis in New Zealand.
- 4.17. The Committee considered that there is an unmet need in patients who fail to respond or are intolerant to biologic treatment.

- 4.18. The Committee considered that some patients continue on current treatments, with diminishing effectiveness, as there are limited funded alternatives, and so there may be a role for treatments with a different mechanism of action.
- 4.19. The Committee noted that ustekinumab had a different mode of action, and considered this may result in some improved efficacy in patients refractory to other biologics. However, members considered that listing ustekinumab would pose considerable fiscal risk to the pharmaceutical budget, given the proposed price and difficulty in limiting access. The Committee recommended that ustekinumab be funded only if cost neutral to adalimumab.

5. TNF Savings Proposal

Application

- 5.1. The Committee considered a paper from PHARMAC staff regarding a proposed savings transaction in the community funded anti-TNF-alpha market (etanercept and adalimumab).

Recommendation

- 5.2. The Committee considered it would be clinically reasonable for etanercept to be the mandated first-line funded TNF for all new patients for currently funded community anti-TNF-alpha indications (excluding Crohn's) and **recommended** PHARMAC staff progress with the proposal.
- 5.3. The Committee **recommended** that PHARMAC consider widening funded access to etanercept as part of the proposal, for example by reducing the required Joint Count for arthritis or PASI scores for psoriasis.
- 5.4. The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 5.5. The Committee noted that adalimumab (Humira, supplied by AbbVie) and etanercept (Enbrel, supplied by Pfizer) are biologic tumour necrosis factor (TNF)-alpha inhibitors currently funded on the Pharmaceutical Schedule in the community for a range of auto-immune conditions. Members noted that adalimumab and etanercept are both funded with similar criteria for patients with rheumatoid arthritis, ankylosing spondylitis, severe chronic plaque psoriasis, psoriatic arthritis, adult onset still's disease and pyoderma gangrenosum and that adalimumab, but not etanercept, is also funded for patients with Crohn's disease and Fistulising Crohn's disease.
- 5.6. The Committee noted that dosing across the funded indications can vary but in general adalimumab is administered 40 mg once fortnightly, whereas etanercept is administered 50 mg once weekly. Members noted that adalimumab and etanercept are both funded as first-line biologic options for patients with severe disease that have not had adequate benefit from, or cannot tolerate, at least 2 other non-biologic funded disease-modifying antirheumatic drugs (DMARDs). Members noted that clinicians and patients currently have the option of funding for either etanercept or adalimumab first line, with the option of switching to the other treatment second line if their disease fails to respond to, or the patient is intolerant of, the first line option.

- 5.7. The Committee noted that both treatments were high cost, with adalimumab currently the Combined Pharmaceuticals Budget's number 1 highest annual expenditure medicine, and etanercept number 4. Members also noted significant growth in the markets and that biosimilar competition for both adalimumab and etanercept is expected in the next few years with biosimilars of etanercept expected to be available before biosimilars of adalimumab.
- 5.8. The Committee noted that PHARMAC staff were currently considering a commercial proposal that, if implemented, would create significant savings in the TNF market. Members noted that the proposal, if implemented, would see etanercept as the mandated first-line funded TNF for all new rheumatology, dermatology, adult onset stills disease and pyoderma gangrenosum patients. Members noted that adalimumab would remain funded for these indications but, for new patients, funding for adalimumab would be limited to patients who have not responded to, or are intolerant of, etanercept (i.e. adalimumab would be available second line only). Members noted that there would be no proposed change to the funding of adalimumab for any existing patients or new patients with Crohn's Disease or Fistulising Crohn's Disease.
- 5.9. The Committee noted that adalimumab currently holds majority TNF market share in New Zealand; however, members noted that in some overseas markets etanercept held majority market share. The Committee considered that whilst there were some differences in the available evidence in some settings between the two treatments, and that some patients, for example children, may prefer the lower frequency of injections with adalimumab, in general there was no clear clinical reason to prefer one treatment over the other in any of their indications other than Crohn's Disease. Members considered that widening access to etanercept may be beneficial for some patients and may assist with implementation of the proposal; however, members noted that there may be some increased cost associated with widening access which PHARMAC needed to consider.
- 5.10. The Committee considered that the proposal for etanercept to be the mandated first line treatment in all funded indications, except Crohn's, was clinically reasonable and members were very supportive of reducing expenditure in the TNF market. Members noted that one possible outcome of the proposal could be a counter-proposal from Abbvie which, if accepted by PHARMAC, may maintain status quo funding at reduced cost.

6. Gemtuzumab ozogamicin for acute myeloid leukaemia

Application

- 6.1. The Committee reviewed an application from a clinician for the funding of gemtuzumab ozogamicin in younger adults with favourable and intermediate-risk acute myeloid leukaemia (AML) in the context of a UK Medical Research Council (UK MRC) co-operative group trial, AML-19.

Recommendation

- 6.2. The Committee **recommended** that funding of gemtuzumab ozogamicin on the Pharmaceutical Schedule for the treatment of favourable and intermediate-risk acute myeloid leukaemia be declined.
- 6.3. The Committee noted that all members were supportive of NZ centres and patients participating in the AML-19 trial and decisions about funding of pharmaceuticals in the context of participation in clinical trials are difficult. Some members of the Committee were of the opinion that unfunded clinical trial treatments should not be funded from the Combined Pharmaceuticals Budget because there are other potential sources of funding to support clinical trials in New Zealand. Members considered PHARMAC should grant a Hospital Medicines List (HML) exemption to enable DHBs to fund gemtuzumab ozogamicin for patients enrolled in the AML-19 clinical trial should the individual DHBs wish to do so.

- 6.4. The Committee reiterated its previous recommendation that PHARMAC review the mechanisms through which unfunded clinical trial treatments including paediatric oncology treatments are considered and funded.
- 6.5. 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*.

Discussion

- 6.6. The Committee noted that this was a funding application for an unregistered medicine in the context of an investigator-led international clinical trial, MRC AML-19, for patients aged 18-60 with acute myeloid leukaemia. Members noted that the Applicant represented the views of the New Zealand Leukaemia Study Group and the Ministry of Health Haematology Working Group.
- 6.7. The Committee noted that acute myeloid leukemia (AML) consists of a group of relatively well-defined hematopoietic neoplasms involving precursor cells committed to the myeloid line of cellular development (ie those giving rise to granulocytic, monocytic, erythroid, or megakaryocytic elements). Members noted that the single most important prognostic factor in AML is cytogenetics with certain cytogenetic abnormalities are associated with very good outcomes (for example, the (15;17) translocation in acute promyelocytic leukemia). About half of AML patients have "normal" cytogenetics; they fall into an intermediate risk group. A number of other cytogenetic abnormalities are known to associated with a poor prognosis and a high risk of relapse after treatment.
- 6.8. The Committee noted that gemtuzumab ozogamicin (Mylotarg, GO) is a monoclonal antibody to CD33 linked to the calicheamicin cytotoxin, ozogamicin. Members noted that CD33 is expressed in most leukemic blast cells but also in normal hematopoietic cells, the intensity diminishing with maturation of stem cells. Members noted that GO was initially approved under an accelerated-approval process by the FDA in 2000 for use in patients over the age of 60 with relapsed AML; or those who are not considered candidates for standard chemotherapy on the basis of early data from the Southwest Oncology Group (SWOG) S0106 study. Members noted however that later data from this study showed that GO did not lead to an increase in the proportion of patients achieving complete remission, nor to improved survival (Petersdorf et al, Blood 2013; 121: 4854–60) and that GO appeared to increase the risk of veno-occlusive disease in the absence of bone marrow transplantation. Members noted that due to these safety concerns GO was withdrawn from the market in 2010.
- 6.9. The Committee noted that the applicant, and the AML-16 trialists, consider that the toxicity of GO is primarily a dosing issue. Members noted that that the SWOG-0106 trial used dosing of 6 mg/m² of GO on day 4 of chemotherapy whereas other studies, including prior MRC AML studies used lower dosing mostly 3 mg/m² on day 1 of chemotherapy.
- 6.10. The Committee reviewed evidence from a meta-analysis of individual patient data from five randomised controlled GO trials (3325 patients), including patients from the SWOG S0106 study and the MRC AML 15 and AML 16 trials (Hills R et al. Lancet Oncol 2014;15:986-996). Members noted that the authors reported that the addition of GO did not increase the proportion of patients achieving complete remission (odds ratio [OR] 0.91, 95% CI 0.77–1.07; p=0.3), however, it did reduce the risk of relapse by 6% at 5 years (50% vs 56%, OR 0.81, 0.73–0.90; p=0.0001), and improved overall survival at 5 years (OR 0.90, 0.82–0.98; p=0.01). Members noted that at 6 years, the absolute survival benefit was especially apparent in patients with favourable cytogenetic characteristics (20.7%; OR 0.47, 0.31–0.73; p=0.0006), but was also seen in those with intermediate characteristics (5.7%; OR 0.84, 0.75–0.95; p=0.005). Patients with adverse cytogenetic characteristics did not benefit (2.2%; OR 0.99, 0.83–1.18; p=0.9). Members

also noted that doses of 3 mg/m² were associated with fewer early deaths than doses of 6 mg/m², with similar efficacy.

- 6.11. The Committee noted that the authors of Hill et al, and an associated editorial (Kharfan MA. Editorial. *Lancet Oncology*, 2014;15:913), concluded that gemtuzumab could help patients with acute myeloid leukaemia of all ages who do not have adverse risk disease, and that a dose of 3 mg/m² should probably be used in future research and clinical practice. Members also noted that evidence from fractionated schedule used in the ALFA-0701 trial (Castaigne et al *Lancet* 2012; 379: 1508–16) suggested that it may produce a greater reduction in relapse than the nonfractionated schedules. Members noted that the fractionated schedule capped each dose at a total of 5 mg (one vial), so patients with a body surface area greater than 1.67 m² would receive a dose lower than 3 mg/m².
- 6.12. The Committee noted that the proposed MRC AML-19 is to be a multicentre randomized controlled, open label, phase III trial comparing several treatment strategies in a multifactorial design in younger patients with AML. Members noted that the trial design is based on the results from the previous AML-15 trial (Burnett et al. *J Clin Oncol* 2011; 29: 369–77) and AML-16 trial (Burnett et al. *J Clin Oncol* 2012; 30: 3924–31). Members noted that the AML-19 study was designed to evaluate several different treatment strategies and investigational agents, members noted that the application for GO was relevant to the subset of patients with favourable cytogenetics wherein four induction chemotherapy schedules are to be compared (namely daunorubicin plus cytarabine (DA) + GO (3 mg/m²) or DA + fractionated GO (3 mg/m² x 2, maximum 5 mg per day) versus fludarabine, cytarabine, G-CSF, and idarubicin (FLAG-Ida) + GO (3 mg/m²) or FLAG-Ida + fractionated GO (3 mg/m² x2, maximum 5mg per day)). Members noted that other arms of the AML-19 study high risk patients will have a different randomisation evaluating the investigational agent CPX-351 and that the trial will also evaluate some different consolidation approaches.
- 6.13. The Committee noted that the applicant noted that the study investigators had secured supply of GO for study participants at a fixed price and that in New Zealand it was anticipated that around 36 patients would be treated with GO in the AML-19 study at a total cost of around \$216,000. Members further noted that the applicant considered that participating in the study would be expected to cure an additional 7-8 patients compared with standard treatment, saving significant health sector costs (>\$1 million) associated with salvage treatments for relapsed AML including bone marrow transplantation and complications. The Committee considered that, given the evidence base and outcomes in previous AML studies, patients would benefit from being enrolled in the AML-19 study and it was highly likely that some patients would be cured that would otherwise not be; however, members considered that it could not determine with certainty the exact number of additional patients that would be cured.
- 6.14. The Committee considered that that the strength and quality of the Hills meta-analysis evidence demonstrating a benefit for GO was questionable given that some of the individual studies gave negative results and the absolute reduction in relapse rate in the meta-analysis was relatively small (6%). However, members considered that the relatively small cost of GO for some patients enrolled in AML-19 would most likely be outweighed by savings to the health sector from a reduction in AML relapses, and considered that there would be other benefits for patients, clinicians and the wider health sector associated with trial participation.
- 6.15. The Committee noted that GO was not commercially available in New Zealand and considered that there was insufficient evidence to support the funding of GO on the Pharmaceutical Schedule, however, members were supportive of NZ centres enrolling AML patients into the AML-19 study to receive GO amongst other treatments noting that historically participation in AML studies that had yielded significant improvements in overall survival rates in New Zealand over the years and this was the standard of care. Members further noted that given the likely benefits from reducing AML relapse rates,

and potential for cure, it was most likely that enrolling patients into the AML-19 study would be cost saving to the health sector.

- 6.16. The Committee noted that it had recently reviewed several funding applications for clinical trial treatments, some of which were also unregistered; members noted that in general it was supportive of NZ centres and patients participating in clinical trials, however, a small majority of members did not consider it appropriate for funding for unfunded clinical trial treatments to come from the Combined Pharmaceuticals Budget. Members considered that PHARMAC should enable centres to participate in clinical trials where funding for unfunded clinical trial treatments could be sourced from the DHB or other funders. Members noted that there were other sources of public funding available for clinical trials in NZ, for example DHBs and Health Research Council funding as well as funding from Non-Government Organisations and the pharmaceutical industry. Members considered PHARMAC should grant a Hospital Medicines List (HML) exemption to enable DHBs to fund GO for patients enrolled in the AML-19 clinical trial should the individual DHBs wish to do so.

7. Pertuzumab for metastatic HER2 positive breast cancer

Application

- 7.1. The Committee considered further information in relation to and application from Roche Products (New Zealand) Ltd for funding of pertuzumab (Perjeta) for the first-line treatment of patients with HER2-positive metastatic breast cancer in combination with trastuzumab and docetaxel.

Recommendation

- 7.2. The Committee **recommended** that pertuzumab be funded with a low priority, for the first line treatment of patients with HER2-positive metastatic breast cancer when used in combination with trastuzumab. The Committee noted that its priority would increase if the price of pertuzumab was reduced to improve its cost effectiveness.
- 7.3. The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 7.4. The Committee noted that it had previously reviewed an application for pertuzumab and related correspondence. The Committee also noted that at its February 2015 meeting that it reiterated its November 2014 recommendation that pertuzumab be funded with low priority and that the Committee review the final overall survival analysis from the CLEOPATRA study once it was published and an updated cost effectiveness analysis had been undertaken.
- 7.5. The Committee reviewed correspondence from the New Zealand Breast Cancer Special Interest Group, dated 23 February 2015, that included the final publication of the CLEOPATRA study data (Swain et al. N Eng J Med 2015;372:724-34). Members also reviewed a letter from Roche, dated 24 February 2015, which discussed and attached the same publication.
- 7.6. The Committee noted that the final publication reported that Progression Free Survival (PFS) and Overall Survival (OS) was significantly improved by first-line therapy with a regimen containing pertuzumab, trastuzumab, and docetaxel, compared with a regimen containing placebo, trastuzumab, and docetaxel. Members noted that median OS was

56.5 months (95% confidence interval [CI], 49.3 to not reached) in the group receiving pertuzumab compared with 40.8 months (95% CI, 35.8 to 48.3) in the group receiving placebo (hazard ratio favouring the pertuzumab group, 0.68; 95% CI, 0.56 to 0.84; P<0.001), a difference of 15.7 months. Members further noted median PFS improved by 6.3 months in the pertuzumab group (hazard ratio, 0.68; 95% CI, 0.58 to 0.80).

- 7.7. The Committee reviewed an updated cost effectiveness analysis of pertuzumab that incorporated this newly-published final data. Members noted that despite the efficacy results appearing impressive, because of its relatively high cost and the need to continue treatment until disease progression, pertuzumab's cost effectiveness remained relatively poor compared with other treatments under consideration.

8. Vismodegib for the treatment of basal cell carcinoma in patients with Gorlin syndrome

Application

- 8.1. The Committee considered an application from Roche Products (NZ) Ltd. for the listing of vismodegib (Erivedge) for the treatment of basal cell carcinoma (BCC) in patients with Gorlin Syndrome.

Recommendation

- 8.2. The Committee **recommended** that the application for listing of vismodegib on the Pharmaceutical Schedule for the treatment of basal cell carcinoma in patients with Gorlin Syndrome be declined.
- 8.3. The Committee **recommended** that NPPA applications for vismodegib should continue to be considered for patients (with or without Gorlin Syndrome) with locally advanced or metastatic BCC where the disease is refractory, or where standard treatments including radiation are contraindicated.
- 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 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

- 8.5. The Committee noted that vismodegib is indicated for the treatment of adult patients with metastatic basal cell carcinoma (mBCC), or with locally advanced basal cell carcinoma (laBCC) where surgery and/or radiation therapy are not appropriate. Members noted that BCC was the most common cancer affecting approximately 50,000 patients per year in New Zealand with risk factors predominantly being sun exposure, light skin and immunosuppression. Members noted that BCC is rarely fatal with most patients effectively cured with cryotherapy, electrodesiccation and curettage (ED&C), surgical excision, topical 5-fluorouracil or imiquimod, radiation therapy, and photodynamic therapy. However, members noted that a small number of patients developed laBCC (around 500 per year) or mBCC (around 50 per year) for whom treatment options are limited, primarily platinum-based chemotherapy, with median survival of around 6 months to 3.6 years. Members noted that this application for vismodegib was for a treatment of laBCC and MBCC in patients with Gorlin Syndrome, a small subset of laBCC/mBCC patients, who are at higher risk of developing BCCs than the general population.
- 8.6. The Committee noted that Gorlin Syndrome, also known as nevoid basal cell carcinoma syndrome, is an inherited condition that increases the risk of developing various

cancerous and noncancerous tumours within multiple body systems. Members noted that it was a rare disorder affecting an estimated 1 in 31,000 people. Members noted that 90% of patients with Gorlin Syndrome develop BCCs and patients typically begin to develop BCCs during adolescence or early adulthood, with the frequency of lesions increasing with age. Members considered that there would be in the region of 20 patients with Gorlin Syndrome who would present with laBCC or mBCC each year.

- 8.7. The Committee noted that Gorlin Syndrome is caused by a germline inactivating mutation in the human homolog of the *Drosophila*, PTCH1, gene, a tumour suppression gene, mutations in which result in a loss of this activity and uncontrolled proliferation. Members noted that PTCH1 gene acts to inhibit the signalling activity of smoothed homologue (SMO) a 7-transmembrane protein which is part of the hedgehog signalling pathway. Members noted that having one mutated copy of the PTCH1 gene is enough to cause some of the features of Gorlin syndrome that are present early in life, including macrocephaly and skeletal abnormalities, but for BCCs and other tumours to develop, a spontaneous mutation in the second copy of the PTCH1 gene must also occur during the person's lifetime. Members further noted that studies have shown that almost all BCCs, not just those from Gorlin's patients, contain genetic mutations in the hedgehog signalling pathway most commonly PTCH1 resulting in aberrant pathway activation and uncontrolled proliferation of basal cells. Members noted that whilst patients with Gorlin Syndrome have the same risk factors for BCCs as the rest of the population they have a higher risk of developing multiple lesions and more aggressive disease.
- 8.8. The Committee noted that vismodegib (Erivedge) is a first-in-class oral small-molecule inhibitor of SMO. Members noted that hedgehog pathway inhibitors such as vismodegib are embryotoxic and/or teratogenic in multiple animal species and are consequently contraindicated in pregnant or nursing women and women of child-bearing potential, unless two reliable methods of contraception are being used during, and for 7 months after, the last dose. Members also noted that male patients must use condoms with spermicide (where available), even after a vasectomy, during sexual intercourse with women while being treated with vismodegib and for 2 months after the last dose and that patients should not donate blood or blood products while on treatment and for 7 months after the last dose.
- 8.9. The Committee considered evidence provided in support of the application from three published studies and one unpublished analysis; 1) a phase 1 trial involving 33 patients with local advanced or metastatic BCC (Von Hoff et al. *N Eng J Med.* 2009;361(12):1164-72), 2) a phase 2 trial (EVIRANCE BCC) (Sekulic A et al *N Engl J Med.* 2012;366(23):2171-9); 3) an unpublished analysis of outcomes in Gorlin patients enrolled in EVIRANCE BCC and a USA expanded access (EAS) trial (Chang et al Poster from 2014 Fall Clinical Dermatology Conference - 33rd Anniversary. October 16-19, 2014; Las Vegas, Nevada), with the EAS study published separately by Chang et al *J Am Acad Dermatol* 2014;70:60-9); and 4) a randomised double-blind, placebo-controlled trial of vismodegib in patients with Gorlin syndrome (Tang et al *N Engl J Med.* 2012;366(23):2180-8.).
- 8.10. The Committee noted that Von Hoff et al. was a phase 1 open-label, non-randomised trial dose finding trial involving 68 patients with a variety of solid tumours, who received vismodegib at 150 mg per day (n=41), 270 mg per day (n=23), or 540 mg per day (n=4) until disease progression, occurrence of intolerable side effects, or study withdrawal. Members noted that the publication focussed on outcomes in the 33 patients enrolled with locally advanced or metastatic BCC (reported together as advanced BCC). Members noted that Overall Response Rate (ORR) based on Response Evaluation Criteria In Solid Tumours (RECIST) in these 33 patients was 58%, with median duration response of 12.8 months. Members noted that based on the maximal plasma concentrations and pharmacodynamic response achieved with vismodigib administered at a dose of 150 mg per day this dose was selected for EVIRANCE BCC (Sekulic A et al.).

- 8.11. The Committee noted that EVIRANCE BCC was a multicentre phase 2 open-label, non-randomised trial that enrolled 104 patients with laBCC or mBCC. Members noted that patients received 150 mg of vismodegib daily, beginning on Day 1, and continuously until disease progression or intolerable toxicity, with dose interruption for up to 4 weeks allowed for patients to recover from toxic effects and for up to 8 weeks before/after surgery. Members noted that patients were enrolled into two cohorts, laBCC (n=71) and mBCC (n=33). Members noted that 22 of the patients enrolled in the study had an underlying diagnosis of Gorlin Syndrome, all of whom were in the laBCC cohort. Members noted that 8 of laBCC patients were excluded from the final efficacy analysis as their BCC was not confirmed in baseline biopsies. Members noted that in the 33 patients with mBCC response rate was 30% (95% CI, 16 to 48; P=0.001), and in the 63 patients with laBCC it was 43% (95% CI, 31 to 56; P<0.001), with complete responses in 13 patients (21%). Members noted that the median duration of response was 7.6 months in both cohorts.
- 8.12. The Committee noted significant toxicity associated with vismodegib in the EVIRANCE BCC study with more than 30% of patients experiencing muscle spasms, alopecia, dysgeusia (taste disturbance), weight loss, and fatigue, serious adverse events reported in 25% of patients and seven deaths occurring (6.7% of patients enrolled in the study). Members noted that the authors concluded that the relationship between the study drug and the deaths was unknown. Members considered that whilst the study reported that 13 (12%) patients discontinued treatment due to adverse events the rate of discontinuation due to toxicity was likely higher noting that in the laBCC group 25% of patients discontinued for 'patient's decision' with the authors speculating that long term, low-grade adverse events (e.g., dysgeusia or muscle cramps) or the perception that the maximal benefit had been achieved may have played a role.
- 8.13. The Committee noted a poster presentation (Chang et al 2014 Fall Clinical Dermatology Conference - 33rd Anniversary. Las Vegas. 2014) of an unpublished analysis comparing outcomes in Gorlin Syndrome and non-Gorlin (sporadic) BCC patients enrolled in the ERIVANCE BCC and a non-randomised Expanded Access Study (EAS) in the USA (Chang et al). Members noted that this analysis showed EVIRANCE and EAS enrolled 22 patients and 7 patients with Gorlin Syndrome, respectively, with BCC overall response rates to vismodegib and observed adverse events in Gorlin Syndrome patients was similar to sporadic patients. Members noted that the poster reported that vismodegib was associated with amenorrhea or irregular menstruation in 43% of women of childbearing potential (2/6 from the EVIRANCE study and 4/8 in the EAS).
- 8.14. The Committee noted evidence from a randomised double-blind, placebo-controlled trial of vismodegib in Gorlin Syndrome patients with a total of at least 10 surgically eligible BCCs present at study entry or removed during the previous 2 years (Tang et al.) Members noted that this study enrolled a different population to population being sought by the supplier for funding. Members noted that 41 patients were randomly assigned 2:1 to receive vismodegib (150 mg per day) (n=26) or placebo (n=15) for a planned treatment period of 18 months. Members noted that the primary end point of the study was 'comparative rate of appearance of new basal-cell carcinomas that were eligible for surgical resection'. Members noted that the study was stopped early at 15 months due to vismodegib significantly reducing the rate of appearance of new surgically eligible BCCs compared with placebo, mean 2 vs 29, median 2 vs. 25 (P<0.001). Members noted that vismodegib also reduced the size of existing BCCs, and reduced the number of surgeries required as part of standard care compared with placebo. The Committee noted that a large proportion of patients in the study, 54%, discontinued vismodegib treatment due to adverse effects, and only 1 of 5 eligible patients was able to continue vismodegib for the planned 18 months. Members noted that when vismodegib treatment was withdrawn, dysgeusia and muscle cramps ceased within 1 month, and scalp and body hair started to regrow within 3 months.
- 8.15. The Committee considered that overall there was weak strength and quality of evidence that vismodegib was efficacious for the treatment of laBCC and mBCC in patients with sporadic disease and Gorlin Syndrome. Members noted in particular that there were no

randomised controlled studies (RCT) in the population being sought for funding, with the only RCT (Tang et al) being a very small study in Gorlin Syndrome patients with surgically eligible BCCs that was stopped early.

- 8.16. The Committee noted that vismodegib was a very high cost medicine and noted that whilst the supplier's application, which limited funding of vismodegib to Gorlin Syndrome patients, reduced the financial impact of funding it, there was no clinically sound reason to differentiate this patient group from other patients with sporadic cases of laBCC or mBCC. Members considered that it was not appropriate to limit funding to just Gorlin Syndrome patients, rather that funding would be best restricted to patients by BCC stage (laBCC or mBCC) and other clinical factors rather than by the underlying cause of the BCC. Members noted that such funding would significantly increase the number of patients treated and costs compared with the estimates provided by the supplier.
- 8.17. The Committee had significant concerns at the level of treatment limiting toxicity of vismodegib and considered that this would limit its usefulness as a long term treatment aimed at delaying disease progression in patients with laBCC or mBCC. The Committee considered that more studies were needed to determine how best to use vismodegib. Members considered that long term vismodegib treatment may be possible with modified dose schedules or that it may be more useful as a short term treatment aimed at improving surgical feasibility and outcomes in patients presenting with invasive/unresectable laBCC or mBCC. The Committee considered that PHARMAC should continue to review NPPA applications for vismodegib, noting there were some settings where it may be useful, for example short term use to improve surgical outcomes in patients with laBCC or mBCC eroding into the brain that is refractory, or contraindicated, to standard treatments including radiation.

9. Bart's Solution

Application

- 9.1. The Committee considered information in relation to requests to fund glucose 4% with sodium chloride 0.18% solution ("Bart's solution") in DHB hospitals.

Recommendation

- 9.2. The Committee **recommended** that the 1000 ml presentation of glucose 4% with sodium chloride 0.18% solution ("Bart's solution") is listed in Part II of Section H of the Pharmaceutical Schedule. The Committee recommended that the 500 ml presentation is not listed in Part II of Section H of the Pharmaceutical Schedule.
- 9.3. The Committee **recommended** that PHARMAC refer the safety concerns raised during consultation on the listing of Bart's solution to the Medicines Adverse Reactions Committee at Medsafe for its review.
- 9.4. The Committee **recommended** that PHARMAC liaise with Medsafe, DHB hospitals and the pharmaceutical supplier to introduce safety measures for this product and other hypotonic parenteral solutions in hospitals including restricting the products to certain areas of the hospital for e.g adult surgical wards and to introduce safety labelling for the products.
- 9.5. The Decision Criteria particularly relevant to this recommendation are: *(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.*

Discussion

- 9.6. The Committee noted that it had reviewed Bart's solution on a number of occasions (February 2013, February 2014 and August 2014). It had previously recommended that Bart's solution be excluded from the Hospital Medicines List (HML) following

consideration of feedback from clinical groups supporting its exclusion on the basis that Bart's solution may be associated with severe and life-threatening adverse effects if inappropriately prescribed, in particular hyponatremia-associated seizures when prescribed as a rehydration solution in children. It was also perceived that only a small number of DHB hospitals were using the product prior to and after the HML came into effect. PHARMAC also received opposing views when it publically consulted on the issue in April 2014.

- 9.7. The Committee noted that PHARMAC had now received two further funding applications from Counties Manukau DHB and the Royal Australasian College of Surgeons requesting that Bart's solution be listed on the HML. The Committee noted that the applications state that Bart's solution would be used as a maintenance fluid in adult surgical patients that are not able to tolerate oral intake. The applications highlighted that Bart's solution is currently still in use in a number of major DHBs around NZ.
- 9.8. The Committee noted that Bart's is preferred over other fluids as a maintenance fluid post-operatively because it provides physiologically appropriate daily sodium and free water requirements. Other funded options would require mixing of different fluid types which may increase nursing workload and potentially result in administration errors. The Committee noted that Bart's with potassium is currently listed on the HML.
- 9.9. The Committee noted that the evidence provided to support the listing of Bart's solution was of weak strength and low quality, mainly from expert opinion rather than direct research evidence (National Institute for Health and Care Excellence (NICE) clinical guidelines 174 (Dec 2013) Intravenous fluid therapy in adults in hospital: guidance.nice.org.uk/cg174 and Powell-Tuck J et al. British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients. Revised 7 March 2011). The Committee noted that the NICE guidelines did not provide any references. The Committee noted that the British Consensus Guidelines recommended that in patients requiring continuing intravenous maintenance fluid, the fluids used be sodium poor and of low enough volume until the patient has returned their sodium and fluid balance over the perioperative period to zero. When this has been achieved, the intravenous fluid volume and content should be those required for daily maintenance and replacement of ongoing losses. The level of evidence quoted by NICE for this recommendation was Level 1b. The Committee however noted that many of the studies referenced for this recommendation were small audits or surveys of clinical practice which did not provide details of the specific intravenous fluids used. The Committee noted that it was unclear if any of the studies included Bart's solution.
- 9.10. The Committee noted that the application also referenced a controlled educational study looking at improving prescription and administration of intravenous fluids in colorectal patients (Gnanasampathan V et al. ANZ J Surg 84 (2014): 932-936). This study did not record adverse events such as electrolyte disturbances or hyponatraemia as an outcome measure and therefore is not relevant to this application.
- 9.11. The Committee noted that there was strong and high quality evidence to support the concern that hypotonic fluids are associated with significant and potentially life-threatening adverse effects in children (Wang J et al. Pediatrics. 2014 Jan; 133(1): 105-13, McNab S et al. Cochrane. 2014 Dec and Foster BA et al. The Journal of Paediatrics. 2014 July; 165(1): 163-16).
- 9.12. The Committee noted that there was also evidence that the use of hypotonic fluids in adults post-operatively was associated with hyponatraemia (Moritz ML et al. Nephrology. 2007; 3: 374-382, Chung H et al. Arch Intern Med Vol 146 1986 Feb, Ayus JC et al. Ann Intern Med 1992; 117: 891-897, Ayus JC and Arieff AI. Chest 1995; 107: 517-521 and Aronson D et al. Am J Kidney Dis 2002; 40: 940-946). The Committee noted however that these studies did not specifically link Bart's solution with hyponatraemia in adults. The Committee considered that all hypotonic solutions carry an inherent risk of hyponatraemia if inappropriately prescribed without regular monitoring of postoperative electrolytes.

- 9.13. The Committee considered that there is very weak evidence to support the benefits of Bart's solution over the other listed intravenous fluids. The Subcommittee however noted that it has been used in a significant number of DHBs prior to the HML and this is likely driven by practice familiarity which would be difficult to change. Therefore, the Committee considered that it would be reasonable to list Bart's solution on the HML. Given the safety issues associated with the solution, the Committee also recommended a number of measures including referring the safety concerns raised regarding Bart's and other hypotonic intravenous fluids to MARC, only listing the 1000ml bag to reduce the chances of it being inadvertently used in children, and to look at introducing other safety measures in liaison with Medsafe, DHB hospitals, and the suppliers.

10. Plerixafor for stem cell mobilisation

Application

- 10.1. The Committee reviewed an application from a clinician for the inclusion of plerixafor (Mozobil) on the Hospital Medicines List (HML) for use in peripheral stem cell mobilisation.

Recommendation

- 10.2. The Committee **recommended** that plerixafor be listed in Part II of Section H of the Pharmaceutical Schedule with high priority, subject to the following access criteria:

Plerixafor

Restricted

Autologous stem cell transplant – haematologist

Both:

1. Patient is undergoing stem cell transplantation; and
2. Either:
 - 2.1 Patient is undergoing G-CSF mobilisation; and
 - 2.1.1 Either:
 - 2.1.1.1 Has a suboptimal peripheral blood CD34 count of $\leq 10 \times 10^6 / L$ on day 5 after 4 days of G-CSF treatment; or
 - 2.1.1.2 Efforts to collect $>1 \times 10^6$ CD34 cells/ kg have failed after one apheresis procedure; or
 - 2.2 Patient is undergoing chemotherapy and G-CSF mobilisation; and
 - 2.2.1 One of the following:
 - 2.2.1.1 Has rising white blood cell counts of $> 5 - 10 \times 10^9 / L$ and a suboptimal peripheral blood CD34 count of $\leq 10 \times 10^6 / L$;
 - 2.2.1.2 Efforts to collect $>1 \times 10^6$ CD34 cells/ kg have failed after one apheresis procedure; or
 - 2.2.1.3 The peripheral blood CD34 cell counts are decreasing before the target has been received.

- 10.3. The Committee **recommended** that PHARMAC seek the advice of the Cancer Treatments Subcommittee (CaTSoP) on whether it would be appropriate to include a limit to the number of doses in the criteria above. The Committee also **recommended** that CaTSoP advice be sought on whether funded access to plerixafor should be limited to one mobilisation attempt per patient.

- 10.4. 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 pharmaceutical 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

- 10.5. The Committee noted that plerixafor has been reviewed by the CaTSoP on a number of occasions, most recently at its March 2015 meeting. The Committee noted the draft minutes from that meeting. The Committee also noted that plerixafor is currently still undergoing Medsafe review for registration in New Zealand and is not yet registered.

- 10.6. The Committee considered the evidence provided in the application and noted that this mainly consisted of case series from different countries reporting in the selective use of this agent in patients who have failed or are failing mobilisation. There were a range of protocols used in different clinical conditions including multiple myeloma, Hodgkin's and non-Hodgkin's lymphoma prior to autologous stem cell transplantation (ASCT) with different outcomes. The Committee considered that there is little evidence looking at long-term outcomes of ASCT in patients treated with plerixafor when compared to those who did not receive the treatment.
- 10.7. The Committee noted that plerixafor could be used as i) a first-line therapy as demonstrated in Phase III studies (DiPersio et al. *J Clin Oncol.* 2009;27(28):4767-73; DiPersio et al. *Blood.* 2009;113(23):5720-6) but this would be associated with a significant cost ; ii) 'pre-emptively' in patients who are failing initial mobilisation attempts; or iii) only in those who have failed mobilisation.
- 10.8. The Committee noted that most of the clinical studies looking at the 'pre-emptive' approach and the associated outcomes were case series (Abhyankar et al. *Bone Marrow Transplant.* 2012 Apr;47(4):483-7, Gopal et al. *J Clin. Apher.* 2012;27(2):81-7; Li et al. *Transfusion.* 2011 Oct;51(10):2175-82). The Committee noted that the restriction criteria proposed by CaTSoP were mainly based on the Abhyankar et al study. The Committee also noted the data from the European compassionate use programme for plerixafor (Hubel et al. *Bone Marrow Transplantation* 2012; 47: 1046-1050), where plerixafor was given to those who failed mobilisation or were at high risk of failing. The Committee noted that 81.6% multiple myeloma patients, 65% non-Hodgkin's lymphoma patients and 81.5% Hodgkin's lymphoma patients were successful in collecting over 2×10^6 CD34+ cells/kg with plerixafor. The Committee noted that similar results were reported for other compassionate access programmes in other countries.
- 10.9. The Committee noted that plerixafor was associated with gastrointestinal upsets or injection site reactions but it was generally well tolerated. The Committee noted that there was one longer term follow up study (Deol et al. *Bone Marrow Transplant.* 2013 Aug; 48(8): 1112–1116) where plerixafor was associated with higher than expected rates of myelodysplastic syndrome (MD) or acute myeloid leukaemia (AML) at 17%. The Committee however noted the results of the Jantunen et al study (*Expert Opin Biol Ther.* 2014 Jun;14(6):851-61) where plerixafor was associated with MD/AML in 3.5% of patients. The same study also commented on longer term reviews that suggest there is a potentially shorter progression free survival in people grafted following mobilisation with plerixafor versus chemotherapy plus G-CSF (granulocyte-colony stimulating factor). The Committee noted that further study was required to investigate the long-term risks associated with plerixafor use.
- 10.10. The Committee noted the results of the cost-utility analysis performed by PHARMAC on plerixafor and considered the assumptions used to be reasonable.
- 10.11. The Committee considered that overall there was good quality and moderately strong evidence to support the effectiveness and safety of plerixafor, but that in the pre-emptive setting currently only case series data are available, although some series have included many patients. Although the evidence in this setting suggests that pre-emptive use is an effective strategy, the Committee considered the evidence to be of poor quality and weak strength as there was no standard definition of 'poor mobilisers' and no control groups for comparison.
- 10.12. The Committee noted that G-CSF +/- chemotherapy were potential funded treatment alternatives for plerixafor but there was a greater failure rate and significant toxicity. The Committee noted that the evidence available so far supports that plerixafor is associated with higher mobilisation rates, better tolerability versus chemotherapy and shorter collection times with less apheresis sessions, which increases predictability for patients and staff. The Committee noted that it was an expensive treatment with limited evidence of its long-term safety, although the Committee noted that these patients had limited alternative treatment options anyway. The Committee considered that the patient

population most likely to benefit from plerixafor would be those where mobilisation has failed or is predicted to fail with G-CSF mobilisation. The Committee considered that there was no evidence to suggest that there were higher mobilisation failure rates in Maori or Pacific peoples in New Zealand.

- 10.13. The Committee considered that the restriction criteria proposed by CaTSoP were reasonable, but asked that PHARMAC seek CaTSoP's advice on whether it would be appropriate to include a limit to the number of doses in the criteria, and also whether funded access to plerixafor should be limited to one mobilisation attempt per patient. The Committee noted that if plerixafor was available, it would potentially lower the threshold for ASCT. The funding of plerixafor would also be associated with a fiscal risk as it is more convenient and probably safer to use than current treatments, particularly chemotherapy mobilisation, and it would be subject to a hospital restriction rather than community Special Authority criteria. The Committee considered that the fiscal risk with the funding of this product could potentially be reduced if it was subject to community Special Authority restrictions, as those restrictions would be easier to enforce.

11. Ivacaftor for cystic fibrosis

Application

- 11.1. The Committee reviewed further information on the cost effectiveness of ivacaftor.

Recommendation

- 11.2. The Committee **recommended** the submission for funding of ivacaftor for the treatment of cystic fibrosis patients with the GD551D gene be declined.
- 11.3. The Decision Criteria particularly relevant to this recommendation are: *(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; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Schedule.*

Discussion

- 11.4. The Committee noted that at its May 2014 meeting it had reviewed an application from Vertex Pharmaceuticals (Australia) Pty for funding ivacaftor for the treatment of patients with cystic fibrosis. The Committee noted that at that time members deferred making a recommendation until data was available from clinical trials evaluating ivacaftor in combination with lumacaftor (VX-809) and until PHARMAC had completed further cost utility analysis on three discreet groups of patients – asymptomatic, bridge-to-transplant, and advanced disease stage. The Committee noted that the Respiratory Subcommittee had reviewed ivacaftor at its April 2014 meeting and made a similar recommendation.
- 11.5. The Committee noted that no clinical trials on the use of ivacaftor in combination with lumacaftor published in peer reviewed journals were available. The Committee noted that results of two phase III clinical trials of ivacaftor in combination with lumacaftor in F508-del CF were publicised by Vertex Pharmaceuticals in a media release in June 2014 but that the results of these clinical trials have not yet been published in peer-reviewed journals. The Committee became aware during the preparation of the minutes for the meeting of the NEJM publication of May 17 2015 DOI: 10.1056/NEJMoa1409547.
- 11.6. The Committee noted that Vertex Pharmaceuticals media release presented point estimates and p values for primary and some secondary outcome variables for each study and for the combined studies. The Committee commented that no confidence intervals were presented for the estimates. The Committee noted that the key apparent finding was that the combination therapy was associated with point estimates of improvement in FEV₁ % of predicted of between 2.6% and 4.0% after 48 weeks, and commented that this compared with the previously minuted point estimates of 10% to

12% in the ivacaftor clinical trials with G551D patients. The Committee noted that, in the pooled analysis, exacerbations decreased from 1.14 per week to 0.7–0.8 per week. The Committee considered that, while the studies could well be of high quality, members were not able to adequately appraise the results, and in particular they did not have confidence intervals available to enable them to evaluate uncertainty around, and the relevance of, the effect.

- 11.7. The Committee considered that its previous assessment of ivacaftor and its possible place in therapy remained unchanged, as no new appreciable information had been supplied. The Committee considered that, while ivacaftor represents a significant improvement in the treatment of cystic fibrosis, it is not a cure and the data is too immature to determine survival benefit yet, although the reported apparent improvement at three years may imply improvement may be expected beyond that time.
- 11.8. The Committee noted cost-utility analysis undertaken by PHARMAC staff for three disease states: early stage, asymptomatic; advanced disease state; and as a bridge-to-lung. Members noted that the best CUA results were reported in the bridge-to-transplant group, as it permitted the attribution of health gains from a lung transplant to ivacaftor. Members considered, in general, that treatment of a patient as early as possible would provide the greatest health gains, albeit at a high cost from lifelong use of ivacaftor.
- 11.9. The Committee considered that although ivacaftor is registered for use in patients 6 years and older, it is most likely that children under 6 years would be prescribed ivacaftor regardless of its registration status, and it is unlikely that these patients would be asymptomatic even at that early age.
- 11.10. The Committee noted that the supplier's CUA model assumed perfect maintenance of health following treatment with ivacaftor. The Committee considered it unlikely that ivacaftor would prevent all further deterioration in health and that it would be more likely that their utility would be similar to that of cystic fibrosis patients who survive medium-term after lung transplantation.
- 11.11. The Committee considered two clinical papers that assessed health utility in lung transplant recipients. Studer et al (*Eur Respir J.* 2004;24:674-685) reviewed the outcomes of lung transplant including survival, function, physiological results, quality of life and cost-effectiveness. Singer et al (*Am J Transplant.* 2005;5:103-109) studied standard gamble utilities in a cohort of stable lung transplant recipients in order to measure utilities for post-transplant health states that could be used to model quality-adjusted survival. The Committee noted that these reviews provided utilities of 0.3 while waiting for a transplant and 0.82 after a bilateral transplant (Studer et al), with a median utility three years after transplant of 0.88 (inter-quartile range 0.5 to 0.99).
- 11.12. The Committee considered that these results validated the supplier's assumptions for health utilities of 0.37 for severe disease and 0.67 for moderate disease, but that it was unlikely that health utility would exceed 0.8 for those with severe or moderate cystic fibrosis after treatment with ivacaftor, as members considered it unlikely that utilities would be better than post bilateral lung transplant.
- 11.13. In relation to defining 'bridge-to-transplant', the Committee considered a consensus update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation on selecting lung transplant patients (Weill et al. *J Heart Lung Transplant* 2015;34:1-15). This defined bridge-to-transplant as "strategies to manage with artificial support an acutely decompensating patient until a suitable organ can be found". The Committee noted this definition is similar to that used in guidelines suggested by the ECORN-CF Study Group (Hirche et al. *Pulm Med.* 2014;2014:621342. doi:10.1155/2014/621342).
- 11.14. The Committee discussed the duration of time that ivacaftor may be used pre-transplant and whether it should be used post-transplant. One case study was discussed (Polenakovik & Sanville. *J Cystic Fibros.* 2013;12:530-1) in which a patient, who was

due to be assessed for a lung transplant, was admitted to hospital with an acute deterioration with FEV₁% falling from around 34% to 24% and needing antibiotics, bilevel positive airway pressure and home oxygen. The patient was treated with ivacaftor for 6 months, after which his FEV₁% was observed to improve to 36% and because he felt better he declined to be assessed for lung transplant. The Committee noted that while the case study did not give an indication on the length of time ivacaftor may be used pre-transplant, it might indicate that some patients may elect not to have a transplant while they are on ivacaftor.

- 11.15. The Committee noted that cost savings are unlikely to occur in the bridge-to-transplant setting as there would be significant costs after a transplant.
- 11.16. The Committee noted information from the Australia and New Zealand cardiothoracic organ transplant registry indicating a median wait for lung transplant (once accepted on the list) of 120 days (in 2012) and 91 (in 2013). The Committee considered that these may be reasonable estimates for the length of time ivacaftor would be used as in this setting, it would be used to improving the physiological state of patients, reducing further decline in lung function and exacerbations.
- 11.17. The Committee commented that other countries had struggled with funding ivacaftor as they were unsure what end point best to model, e.g. reduction in FEV₁, improvement post-transplant, or improvement in survival rates. The Committee considered that while ivacaftor shows benefit in the treatment of cystic fibrosis patients with the G551D-CFTR mutation, its cost remains prohibitive and there is no long term data to determine a survival benefit. The Committee considered that, from the as yet unpublished (in peer-reviewed journals) information that is available on lumacaftor, it appears that lumacaftor and ivacaftor in F508-del CF, may be less effective than ivacaftor in G551-D CF.

12. Indacaterol maleate/glycopyrronium for chronic obstructive pulmonary disease

Application

- 12.1. The Committee reviewed an application from Novartis New Zealand Limited for the inclusion of ULTIBRO Breezhaler (indacaterol maleate with glycopyrronium bromide) on the Pharmaceutical Schedule for the treatment of chronic obstructive pulmonary disease.

Recommendation

- 12.2. The Committee **recommended** indacaterol maleate with glycopyrronium bromide be funded with a low priority.
- 12.3. 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 Māori 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; 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

- 12.4. The Committee noted that indacaterol maleate with glycopyrronium bromide is a combination fixed dose long-acting muscarinic antagonist (LAMA) with a long-acting beta2-adrenoceptor agonist (LABA) combination registered for the once daily maintenance treatment of chronic obstructive pulmonary disease (COPD). The Committee noted the application was for funding indacaterol maleate with glycopyrronium bromide under the same Special Authority criteria pertaining to tiotropium and glycopyrronium. The Committee noted that indacaterol/glycopyrronium is an inhalation powder capsule containing the equivalence of 110 µg of indacaterol and 50

µg of glycopyrronium. The Committee noted members had recently recommended declining an application for funding the umeclidinium with vilanterol LAMA/LABA combination supplied by GSK.

- 12.5. The Committee noted there is broad consensus on the management of COPD using the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2014) strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (updated 2014) (http://www.goldcopd.org/uploads/users/files/GOLD_Report2014_Feb07.pdf) which defines 4 stages of COPD. The Committee noted those stages were defined as category A, mild COPD; category B, moderate COPD; category C, severe COPD and category D, very severe COPD.
- 12.6. The Committee noted that smoking cessation (if applicable) continues to be the most important intervention for COPD, as it has been shown to be effective in slowing disease progression. The Committee noted that none of the pharmacotherapies routinely used in the treatment of COPD have conclusively shown to modify long-term deterioration in lung function so treatment is primarily aimed at relieving symptoms, reducing the frequency of exacerbations and improving general health status and exercise tolerance.
- 12.7. The Committee noted that the indacaterol with glycopyrronium combination has been well studied with at least 8 published and 4 ongoing, unpublished randomised trials of approximately 10,000 patients (collectively known as the IGNITE studies). The Committee noted three key studies: SHINE (Bateman ED. *Eur Respir J.* 2013;42:1484-94); SPARK (Wedzicha JA. *Lancet Respir Med.* 2013;1:199-209) and ILLUMINATE (Vogelmeier CF. *Lancet Respir Med.* 2013;1:51-60).
- 12.8. The Committee noted that in these Phase III studies indacaterol with glycopyrronium significantly improved bronchodilation versus indacaterol, glycopyrronium and tiotropium alone and the fluticasone with salmeterol fixed dose ICS/LABA combinations. Members noted that improvements in lung function were rapid in onset, were maintained during long-term treatment and were generally associated with significant improvements in dyspnoea, health status, COPD exacerbation risk, patient symptoms, and rescue medication use. The Committee noted that the SHINE and ILLUMINATE studies suggested that indacaterol with glycopyrronium offered greater symptomatic relief in patients with moderate to severe disease with a low exacerbation risk and that indacaterol with glycopyrronium may offer greater symptomatic relief than tiotropium and the ICS/LABA fluticasone with salmeterol. The Committee noted that the SPARK study in patients with severe or very severe disease with a high risk of exacerbations suggested that indacaterol with glycopyrronium was more effective than glycopyrronium as a single agent in preventing moderate to severe exacerbations and - that the combination therapy may offer more symptomatic relief than LAMA monotherapy.
- 12.9. The Committee also noted a study by Wedzicha JA et al (*Respir Med.* 2014;108:1498-507) reviewing the safety of indacaterol with glycopyrronium. Data from 11,404 patients with COPD were pooled from 14 clinical studies with a duration greater or equal to three months with at least two of the treatment groups indacaterol 110 µg with glycopyrronium 50 µg, indacaterol 110 µg, glycopyrronium 50 µg, tiotropium 18 µg or placebo. The Committee noted this study showed that the overall hazard ratio for indacaterol with glycopyrronium versus placebo showed no significant increase in the overall risk for death (HR [95% confidence interval]; 0.93 [0.34-2.54]); cardiovascular and cerebrovascular events (0.60[0.29-1.24]); major adverse cardiac events (1.04[0.45-2.42]); pneumonia (1.10[0.54-2.51]); and atrial flutter/fibrillation (1.03[0.49-2.18]). Members noted that COPD exacerbations were reduced at (0.60[0.40-0.91]) and that similar results were observed for indacaterol, glycopyrronium and tiotropium versus placebo for overall risk and in analysed subgroups.
- 12.10. The Committee considered that the strength and quality of the evidence included in the submission by the supplier was good and superior to that presented with a COPD

product reviewed at an earlier meeting. The Committee also considered that the documentation provided by the supplier was well presented.

- 12.11. The Committee considered that the indacaterol with glycopyrronium combination would have the same or similar therapeutic effect as a LAMA plus a LABA. However, some patients may receive a benefit due to the greater convenience. Some members of the Committee expressed concern regarding the high use of inhaled corticosteroids in COPD and considered that listing the combination LAMA/LABA product may help to decrease the use of ICS in COPD patients. The Committee considered that some patients currently on single agent LAMA or LABA would potentially switch to indacaterol with glycopyrronium combination if it were available as a funded alternative.
- 12.12. The Committee recommended that indacaterol maleate with glycopyrronium bromide be listed in the Pharmaceutical Schedule with a low priority and recommended that all LAMA/LABA products be assessed by the Respiratory Subcommittee in order to determine where these agents demonstrate the maximal benefit and safety in COPD management.

13. Macitentan for pulmonary arterial hypertension

Application

- 13.1. The Committee considered a funding application from Actelion Pharmaceuticals Ltd. for the listing of macitentan (Opsumit) in the Pharmaceutical Schedule for treatment in patients with pulmonary arterial hypertension (PAH) belonging to WHO clinical classification Groups I, IV, and V, in NYHA/WHO functional class III or IV.

Recommendation

- 13.2. The Committee **recommended** that macitentan (Opsumit) be listed in the Pharmaceutical Schedule for patients with PAH with the same restrictions as bosentan, with a low priority.
- 13.3. The Committee **recommended** that macitentan (Opsumit) should not be used in children as there is no currently published research that has investigated paediatric use of macitentan.
- 13.4. The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iv) The clinical benefits and risks of pharmaceuticals; and (v) the cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*

Discussion

- 13.5. The Committee noted that macitentan is a dual Endothelin Receptor Antagonist (ERA) administered orally in a once daily formulation. The Committee also noted that the alternative dual ERA that is currently listed in the Pharmaceutical Schedule is bosentan.
- 13.6. The Committee noted that macitentan has been approved by the Food and Drug Administration and the European Medicines Agency, and recommended for listing by the Canadian Agency for Drugs and Technologies in Health, Pharmaceutical Benefits Advisory Committee (Australia) and Scottish Medicines Consortium.
- 13.7. The Committee noted that two recently published meta-analyses into the effectiveness of PAH treatments (Zheng et al., *Pulm Pharmacol Ther.* 2014, 29 (2):241-249 and Zheng et al., *Eur J Clin Pharmacol.* 2014, Jan; 70 (1): 13-21) reported a survival benefit for phosphodiesterase type 5 inhibitors (PDE5I's) and intravenous prostanoids alone, while ERAs were effective in reducing clinical worsening.

- 13.8. The Committee considered, SERAPHIN, a randomised, placebo-controlled, multicentre, event driven trial in 742 patients with PAH, all belonging to group 1 of the WHO (Venice) clinical classification (iPAH, CHD, CTD, drugs/toxin-induced PAH, HIV) as the main clinical evidence to support the application. The Committee noted that no head to head studies have been conducted against currently funded alternatives [REDACTED]
- 13.9. The Committee considered the evidence provided in the SERAPHIN Clinical Study to be of both moderate quality and strength (level 1B). There was a relatively high risk of bias and overestimation of treatment effect due to the study design. Members noted the involvement of Actelion in designing and conducting all statistical analysis, and the assistance of a professional medical writer for the final publication in NEJM 2013. Members noted that sicker patients were not excluded from the study. The Committee considered that there was a high level of premature discontinuation in SERAPHIN, in both the placebo and treatment groups, with patients not followed to the end of the trial.
- 13.10. The Committee noted that the composite primary end points, such as those used in SERAPHIN, are commonly utilised in cardiovascular studies and are in line with international recommendations.
- 13.11. The Committee noted that the study was not sufficiently powered to demonstrate an effect on mortality, with the macitentan 10mg dose providing a statistically non-significant relative risk reduction in the occurrence of death from all causes.
- 13.12. The Committee noted that worsening of pulmonary arterial hypertension was the most frequent primary end-point event. The Committee noted that there was a significant reduction, with wide confidence intervals, in the composite primary endpoint for the macitentan 10mg group compared to placebo, with a hazard ratio of 0.55 (97.5% CI 0.39-0.76; $p < 0.001$). The Committee noted that there was also a significantly reduced rate of hospitalisation in the macitentan 10mg group compared to placebo (HR 0.5; 97.5% CI 0.34-0.75; $p < 0.001$).
- 13.13. The Committee noted an increase in 6 Minute Walk Distance (6 MWD), that was statistically significant, and WHO functional class, when comparing macitentan 10mg with placebo. The Committee were concerned about size of a clinically relevant improvement in 6MWD, in relation to the confidence intervals of the study.
- 13.14. The Committee considered that macitentan improved mean quality of life scores, with significant improvements in all measured domains except for general health perception. The Committee noted that in a subset of patients who underwent cardiac catheterisation during the study, there was a median reduction in pulmonary vascular resistance of 36.5% (CI 21.7-49.2%) and an increase in cardiac index of 0.58 L/min/m² (CI 0.28 – 0.93 L/min/m²) in the patients given macitentan 10mg (n=57) versus placebo (n=67).
- 13.15. The Committee considered that there may be a survival benefit compared to bosentan; however, it was unclear from the published results how many deaths attributed to placebo at the end of the trial, actually occurred in patients receiving open label macitentan.
- 13.16. The Committee considered that macitentan had a comparable mode of action to bosentan, and agreed with the supplier's that it may eventually replace bosentan, in adults, unless newer agents became available.
- 13.17. The Committee considered that the superior pharmacodynamic and pharmacokinetic characteristics of macitentan, in comparison to currently funded ERAs, may be beneficial. Members considered that the reduced potential for drug interactions and lower incidence of side effects was superior to currently funded ERAs. Members considered that there may be a reduced frequency of liver function testing in comparison to bosentan due to a reduced risk of hepatotoxicity.

- 13.18. The Committee considered that treatment-naïve (incident) patients appeared to have greater clinical benefit from macitentan compared to treatment experienced (prevalent) patients. The Committee suggested that macitentan would replace bosentan in treatment naïve patients; however stable patients would remain on bosentan or ambrisentan as is the situation in Australia.
- 13.19. The Committee considered that the supplier may have underestimated the rate of switch from bosentan to macitentan and also the increasing prevalence in New Zealand of diagnosed PAH patients. The Committee did not agree with the applicants request that macitentan should be listed for initial treatment in combination with sildenafil in WHO Functional Class III-IV patients.
- 13.20. The Committee noted that at present, PAH treatments are funded for patients with functional class III or IV, with applications being considered in cases where there is clear evidence of disease progression (defined as a deterioration in performance of the 6MWT or deterioration in haemodynamic variables) despite current therapy in functional class II.
- 13.21. Members considered new drugs with novel mechanisms of action for combination use would be more advantageous.
- 13.22. The Committee noted that bosentan is no longer on patent and therefore decreasing costs may enable earlier access to ERA therapy.

14. Denosumab for osteoporosis

Application

- 14.1. The Committee considered a reapplication from Amgen for the funding of denosumab (Prolia) for the treatment of osteoporosis in postmenopausal women.

Recommendation

- 14.2. The Committee **recommended** that denosumab be funded subject to Special Authority criteria and Hospital Medicines List restrictions as outlined below for the treatment of osteoporosis in postmenopausal women who have received inadequate benefit from oral treatments and for whom zoledronic acid is contraindicated because of renal impairment, with a medium priority.

Initial application from any relevant practitioner. Approvals valid without further renewal unless notified for applications meeting the following criteria:

All of the following:

- 1 The patient is a postmenopausal woman with severe, established osteoporosis; and
- 2 Any of the following:
 - 2.1 History of one significant osteoporotic fracture demonstrated radiologically and documented bone mineral density (BMD) ≥ 2.5 standard deviations below the mean normal value in young adults (i.e. T-Score ≤ -2.5) (see Note); or
 - 2.2 History of one significant osteoporotic fracture demonstrated radiologically, and either the patient is elderly, or densitometry scanning cannot be performed because of major logistical, technical or pathophysiological reasons. It is unlikely that this provision would apply to many patients under 75 years of age; or
 - 2.3 History of two significant osteoporotic fractures demonstrated radiologically; or
 - 2.4 Documented T-Score ≤ -3.0 (see Note); or
 - 2.5 A 10-year risk of hip fracture $\geq 3\%$, calculated using a published risk assessment algorithm (e.g. FRAX or Garvan) which incorporates BMD measurements (see Note); or
 - 2.6 Patient has had a Special Authority approval for alendronate (Underlying cause - Osteoporosis) or raloxifene; and

- 3 The patient has experienced at least one symptomatic new fracture after at least 12 months' continuous therapy with a funded antiresorptive agent at adequate doses (see Notes); and
- 4 Zoledronic acid is contraindicated because the patient's creatinine clearance is less than 35 mL/min; and
- 5 The patient must not receive concomitant treatment with any other funded antiresorptive agent for this condition or teriparatide.

Notes:

- a) BMD (including BMD used to derive T-Score) must be measured using dual-energy x-ray absorptiometry (DXA). Quantitative ultrasound and quantitative computed tomography (QCT) are not acceptable.
- b) Evidence suggests that patients aged 75 years and over who have a history of significant osteoporotic fracture demonstrated radiologically are very likely to have a T-Score ≤ -2.5 and, therefore, do not require BMD measurement for treatment with denosumab.
- c) Osteoporotic fractures are the incident events for severe (established) osteoporosis and can be defined using the WHO definitions of osteoporosis and fragility fracture. The WHO defines severe (established) osteoporosis as a T-score below -2.5 with one or more associated fragility fractures. Fragility fractures are fractures that occur as a result of mechanical forces that would not ordinarily cause fracture (minimal trauma). The WHO has quantified this as forces equivalent to a fall from a standing height or less.
- d) A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.
- e) Antiresorptive agents and their adequate doses for the purposes of this Special Authority are defined as: risedronate sodium tab 35 mg once weekly; alendronate sodium tab 70 mg or tab 70 mg with cholecalciferol 5,600 iu once weekly; raloxifene hydrochloride tab 60 mg once daily. If an intolerance of a severity necessitating permanent treatment withdrawal develops during the use of one antiresorptive agent, an alternate antiresorptive agent must be trialed so that the patient achieves the minimum requirement of 12 months' continuous therapy

- 14.3. 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.*

Discussion

- 14.4. The Committee noted that it had reviewed an application from Amgen to fund denosumab for postmenopausal women with osteoporosis at its May 2012 meeting, and had recommended that the application be declined pending further information about the long-term safety of treatment with denosumab. The Committee noted that in July 2014, the Endocrinology Subcommittee of PTAC requested that PTAC re-review denosumab in light of the availability of longer-term safety data, and that the supplier had subsequently provided additional safety data for review.
- 14.5. The Committee noted that hip fractures are associated with significant morbidity and mortality, which has been extensively documented, including in the New Zealand setting (e.g. Weatherall M. N Z Med J. 1994;107:308-9).
- 14.6. The Committee noted that it had previously reviewed the key clinical studies for denosumab (Cummings et al. New Engl J Med 2009;361:756-65; Brown et al. J Bone Mineral Res 2009;24:153-61; Kendler et al. J Bone Mineral Res 2010;25:72-81; Freemantle et al. Osteoporosis Int 2011;22:1725-35) and considered that there was reasonable evidence to suggest that denosumab reduces vertebral and nonvertebral fractures in postmenopausal women with osteoporosis compared with placebo. However this was not the indication requested by either the supplier or the Subcommittee, the supplier is seeking funding of denosumab as a second-line treatment. The Committee noted that there was no head-to-head evidence on fracture risk reduction with denosumab compared with existing therapy used in the New Zealand setting.

- 14.7. The Committee noted that the key safety data for denosumab come from an extension of the FREEDOM trial, a randomised controlled trial comparing denosumab 60 mg every 6 months with placebo over three years of treatment in women with post-menopausal osteoporosis (Cummings et al. *New Engl J Med* 2009;361:756-65). In the extension trial, women from the FREEDOM denosumab group continued to receive denosumab (long-term group) and women from the FREEDOM placebo group were given denosumab (crossover group). The trial still has two years to run.
- 14.8. The Committee noted that three (crossover) and six-year (long-term) data from the trial were published in 2013 (Bone et al *J Clin Endocrinol Metab.* 2013;98(11):4483-92). The Committee noted that the extension group experienced further increases in bone mineral density (BMD) – although the Committee was unsure as to the clinical significance of this – as well as maintaining reductions in bone turnover markers and reductions in fracture risk. The Committee noted that annual incidence rates of adverse events were similar over time in the extension study, surmising that the prevalence of patients experiencing any adverse events during the study would consequently have accumulated, rising over time (i.e. from perhaps a near-linear cumulative incidence of events). The Committee noted that six participants experienced osteonecrosis of the jaw during the study.
- 14.9. The Committee noted that up to eight years of safety data from the trial are now available, although these have not yet been published and the supplier had provided the Synopsis Clinical Study Report and key abstract publications. Women in the long-term group received 8 years of denosumab (3 years in FREEDOM and 5 years in the extension); women in the cross-over group received 5 years of denosumab (3 years of placebo in FREEDOM and 5 years of denosumab in the extension). The Committee noted that, through year 5 of the extension, 3004 (66%) of the 5928 patients eligible for the extension remained in the study. The Committee noted that no new safety concerns had emerged from the FREEDOM extension study, with the exposure-adjusted subject incidences of adverse events (rates per 100 subject years) in the long-term denosumab group remaining relatively stable over time. Again, the Committee noted that, consequently, the prevalence of adverse events in study participants increased over time.
- 14.10. The Committee noted that it is unclear what the safety profile would be for the requested group of patients meeting this indication, as they would have already been exposed to several lines of therapy, possibly for many years. Therefore, without safety data in the population requested, notwithstanding the extension data in a much earlier disease state, the Committee considered that there are still significant uncertainties in the safety of the use of denosumab in this setting.
- 14.11. The Committee noted the supplier's comment that available nonclinical and clinical evidence to date has shown no increased risk of, or progression of, malignancy with denosumab. The Committee considered that pharmacovigilance is still required.
- 14.12. The Committee noted a meta-analysis assessing the safety of denosumab in postmenopausal women with low BMD (Zhou et al. *Int J Clin Exp Pathol.* 2014;7:2113-22), which reported that denosumab treatment significantly decreased the risk of non-vertebral fracture compared to placebo (RR=0.86, 95% CI=0.74-1.00, p=0.05) but increased the risk of serious adverse events related to infection (RR=1.23, 95% CI=1.00-1.52, p=0.05). However, no difference between the safety of denosumab and bisphosphonates was found.
- 14.13. The Committee noted a randomised, open-label study in which 870 postmenopausal women aged ≥ 55 years received denosumab 60 mg subcutaneously every 6 months or risedronate 150 mg orally every month for 12 months (Roux et al. *Bone.* 2014;58:48-54). At month 12, denosumab significantly increased BMD compared with risedronate at the total hip (2.0% vs 0.5%), femoral neck (1.4% vs 0%), and lumbar spine (3.4% vs 1.1%; p<0.0001 at all sites). Denosumab significantly decreased sCTX-1 (a serum marker of bone resorption) compared with risedronate at month 1 (median change from baseline

of -78% vs -17%; $p < 0.0001$) and month 6 (-61% vs -23%; $p < 0.0001$). However, the Committee was unclear as to the relationship of this surrogate marker to fracture risk in this setting and, therefore, this evidence was not used to inform the Committee's recommendation. Overall and serious adverse events were similar between groups.

- 14.14. The Committee noted that while denosumab resulted in significantly greater increase in BMD and reduction in bone turnover markers than alendronate in a randomised controlled trial in 1189 postmenopausal women (reported in Brown et al. *J Bone Mineral Res* 2009;24:153-61), denosumab was no more effective than alendronate in reducing clinical fractures in this trial. The overall safety profile was similar for both treatments.
- 14.15. Overall, the Committee considered that its previous safety concerns had not been addressed for this population; however, the Committee felt reassured by the longer-term data suggesting that the risk of malignancy and infection from denosumab in this earlier-use population is similar to its use in the shorter-term studies. The Committee noted that denosumab has an adverse risk profile including osteonecrosis of the jaw and/or increased fracture risk (secondary to poor bone remodelling). The risk of side effects in a much more severe group, as requested, for this indication and where no evidence exists for fracture risk reduction or safety with this agent was noted. The Committee commented that despite a malignancy risk not having emerged from the longer-term trial, denosumab carries a theoretical risk of infection and malignancy. The Committee considered that a much larger patient pool would need to be followed up for an increase in malignancy risk to be detected.
- 14.16. The Committee considered that denosumab would provide a similar benefit to oral bisphosphonate treatments, in terms of fracture reduction. However, denosumab would be used as a second-line treatment. The Committee also noted that denosumab was significantly more expensive than the funded bisphosphonate treatments and, unlike bisphosphonate treatment, the benefits of denosumab ended with cessation of use – therapeutic benefit is dependent on ongoing adherence to treatment. The Committee considered that patients would need to take denosumab long-term, potentially for the remainder of their life. In contrast, the Committee noted that emerging evidence suggests that only two or three doses of zoledronic acid may be needed to provide long-term benefit.
- 14.17. The Committee noted that there was a large range of funded osteoporosis treatments currently, with the most commonly used being risedronate, alendronate and zoledronic acid. The Committee considered that the greatest unmet need at present was for patients who had not responded adequately to oral treatments and who could not take zoledronic acid because of renal impairment. The Committee noted that contraindication to zoledronic acid, rather than intolerance, should be used when outlining the restrictions on denosumab, to ensure it is used appropriately.
- 14.18. The Committee considered that it would be reasonable to restrict denosumab to this patient group based on cost. The Committee considered that, under such restrictions, the number of denosumab patients could be very large, potentially more than 10% of the total treated patient pool.
- 14.19. The Committee noted that access to dual-energy x-ray absorptiometry (DXA) scans is limited in some DHBs and incurs a cost in primary care. The Committee requested that PHARMAC staff seek advice from the Endocrinology Subcommittee as to whether the DXA-related criteria for alendronate, zoledronic acid, raloxifene and teriparatide remain appropriate.

15. TNF-alpha Inhibitors for Behcet's disease

Application

- 15.1. The Committee considered the minutes of the Dermatology and Ophthalmology Subcommittees of PTAC in relation to a clinician's application to fund tumour necrosis factor (TNF)-alpha inhibitors for patients with treatment-refractory Behçet's disease.

Recommendation

- 15.2. The Committee **recommended** that the funding of infliximab should be widened to include ocular and non-ocular manifestations of Behçet's disease, subject to the following Hospital Medicines List (HML) restrictions, with a medium priority:

Initiation – severe Behçet's disease

Re-assessment required after 3-4 months

All of the following:

- 1 The patient has severe Behçet's disease which is significantly impacting the patient's quality of life (see Notes); and
- 2 Either:
 - 2.1 The patient has severe ocular, neurological and/or vasculitic symptoms and has not responded adequately to one or more treatment(s) appropriate for the particular symptom(s) (see Notes); or
 - 2.2 The patient has severe gastrointestinal, rheumatologic and/or mucocutaneous symptoms and has not responded adequately to two or more treatment appropriate for the particular symptom(s) (see Notes); and
- 3 The patient is experiencing significant loss of quality of life.

Notes.

a) Behçet's disease diagnosed according to the International Study Group for Behçet's Disease. Lancet 1990;335(8697):1078-80. Quality of life measured using an appropriate quality of life scale such as that published in Gilworth et al J Rheumatol. 2004;31:931-7.

b) Treatments appropriate for the particular symptoms are those that are considered standard conventional treatments for these symptoms, for example intravenous/oral steroids and other immunosuppressants for ocular symptoms; azathioprine, steroids, thalidomide, interferon alpha and ciclosporin for mucocutaneous symptoms; and colchicine, steroids and methotrexate for rheumatological symptoms.

Continuation – Severe Behçet's disease

Both:

- 1 Patient has had a good clinical response to initial treatment with measurably improved quality of life; and
- 2 Infliximab to be administered at doses no greater than 5 mg/kg every 8 weeks.

- 15.3. The Committee further **recommended** that, if access to infliximab was widened as outlined above, access to adalimumab be similarly widened (if adalimumab was priced similarly infliximab), or widened to allow its use in patients with Behçet's disease who are intolerant to infliximab or who have received inadequate benefit from infliximab (if adalimumab was more expensive than infliximab), with a medium priority.

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

- 15.5. The Committee **recommended** that etanercept not be funded for Behçet's disease.

- 15.6. The Decision Criterion particularly relevant to this recommendation is: *(iv) The clinical benefits and risks of pharmaceuticals.*

Discussion

- 15.7. The Committee noted that in August 2012 it had reviewed a clinician's application to fund TNF-alpha inhibitors for the treatment of patients with Behçet's disease who are

refractory to conventional therapy. The Committee noted that it had recommended that a TNF-alpha inhibitor should be listed in the Pharmaceutical Schedule for patients with severe Behçet's disease refractory to conventional therapy, with a medium priority. Members considered that although the evidence for efficacy of the individual TNF-alpha inhibitors was variable, it is likely they would all provide similar outcomes; therefore the Committee recommended that the funded TNF-alpha inhibitor should be the one associated with the lowest cost. The Committee further recommended the application be referred to the Dermatology and Ophthalmology Subcommittees for advice on specific Special Authority criteria and if they had any preference for the specific TNF(s) to be funded.

- 15.8. The Committee noted that in July 2013 infliximab had been listed on the Hospital Medicines List (HML) for severe and chronic treatment-resistant ocular inflammation, which would include patients with Behçet's disease and ocular symptoms.
- 15.9. The Committee noted that in December 2013 the Dermatology Subcommittee considered that infliximab would be the preferred treatment option and recommended listing infliximab first line as a high priority with entry and exit restrictions. The Subcommittee also recommended listing adalimumab second line as a medium priority with entry and exit restrictions. No specific restrictions were proposed, nor was it clear what manifestations of Behçet's disease the Subcommittee considered should be covered by the restrictions.
- 15.10. The Committee noted that in October 2014 the Ophthalmology Subcommittee recommended that infliximab continue to be available on the HML as the first-line TNF-alpha inhibitor for patients with ocular Behçet's disease who were refractory to conventional therapy. The Subcommittee noted this patient group is already accessing infliximab on the HML through the ocular inflammation criteria. The Subcommittee recommended that funded access to adalimumab be widened to include patients with Behçet's disease and who were refractory to conventional therapy if cost neutral to infliximab. The Subcommittee recommended funding adalimumab for patients with Behçet's disease and who were refractory to conventional therapy as a second-line TNF treatment if infliximab had failed, with a high priority, subject to Special Authority criteria. The Subcommittee recommended that the application to fund etanercept for Behçet's disease be declined due to weak evidence and reduced efficacy compared to infliximab and adalimumab. The Subcommittee did not discuss non-ocular criteria.
- 15.11. The Committee noted that both Subcommittees expressed a preference for infliximab as the first-line TNF-alpha inhibitor, with adalimumab as a second line option for patients who have not responded to infliximab.
- 15.12. The Committee noted several publications on the use of TNF-alpha inhibitors in Behçet's disease that were not previously reviewed by the Committee (or where the Committee had only reviewed an abstract), including:

Takeuchi et al. *Ophthalmology* 2014;121:1877-84

Cantini et al. *Biologics: Targets and Therapy* 2012;6:5-12

Lee et al. *Inflamm Bowel Dis* 2013;19:1833-8

Bawazeer et al. *Ocul Immunol Inflamm* 2010;18:226-232

Olivieri et al. *Clin Exp Rheumatol* 2011;29:S54-7

Diaz-Llopis et al, *Ophthalmology* 2012;119:1575-81

- 15.13. The Committee noted that the above publications and the evidence previously reviewed by the Committee generally supported a modest benefit from TNF-alpha inhibitors in

Behçet's disease, although the evidence was of poor quality and moderate strength, with no prospective randomised controlled trials (RCTs).

- 15.14. The Committee considered that from the limited available evidence infliximab and adalimumab appeared to provide similar benefits in Behçet's disease; however, the Committee noted that there was more published evidence for infliximab and supported the Dermatology and Ophthalmology Subcommittees' view that infliximab was a reasonable first-line TNF-alpha inhibitor. The Committee considered that adalimumab would be a reasonable second-line treatment option (or first line option in addition to infliximab if it was no more expensive than infliximab), noting the Ophthalmology's estimate that 20% of patients may not respond to infliximab. The Committee considered that the criteria proposed by the Ophthalmology Subcommittee for adalimumab as a second-line treatment option were reasonable.
- 15.15. The Committee considered that there was insufficient evidence to support a recommendation to fund etanercept for Behçet's disease, particularly for the ocular form.
- 15.16. The Committee considered that the likely dosing schedule for infliximab in Behçet's disease would be 5 mg/kg on weeks 0, 2 and 6, followed by 5 mg/kg every 8 weeks. The dose regimen for adalimumab would be 40 mg per fortnight. The Committee considered that the dose regimen for both treatments would be the same regardless of which symptoms of Behçet's disease they were being used to treat.
- 15.17. The Committee considered that there could be approximately 25 patients per year with Behçet's disease who would meet the proposed criteria for infliximab, although this may be an underestimate.
- 15.18. The Committee considered that based on a study by Bernabe et al (Rheumatology 2010;49:2165-2171), quality of life in patients with Behçet's disease is poor and appears to be similar to that experienced by patients with multiple sclerosis and active arthritis. The Committee considered that it is reasonable to assume that improvement of Behçet's disease-related symptoms would improve the quality of life in these patients. The Committee considered that in the absence of New Zealand-specific evidence, it would be reasonable to use the Bernabe et al 2010 study as a proxy to estimate the health-related quality of life for New Zealand Behçet's disease patients.
- 15.19. The Committee noted that comparator treatments would depend on the particular symptom manifestations of Behçet's disease. For example, colchicine, thalidomide and interferon alpha could be used as comparators for mucocutaneous lesions but for vital organ involvement other immunosuppressant treatments are valid comparators, for example intravenous cyclophosphamide, ciclosporin, methotrexate and azathioprine. The Committee noted that lack of a clear treatment algorithm makes determination of appropriate comparator treatment(s) difficult; however, for the purposes of PHARMAC's analyses the highest and lowest cost alternative treatment options could be used in the sensitivity analysis.
- 15.20. The Committee considered that TNF-alpha inhibitors would likely be used in combination with other immunosuppressants, although the choice of other agents would depend on the symptom being treated.
- 15.21. The Committee considered that Arida et al (Semin Arthritis Rheum 2011;41:61-70) would be reasonable to use to inform PHARMAC's modelling in terms of response rates for different presentations of Behçet's disease, and that Lee et al (Inflamm Bowel Dis 2013;19:1833-8) might also be useful with respect to gastrointestinal response rates.
- 15.22. The Committee noted that Behçet's disease is associated with increased mortality (Savey et al. Orphanet Journal of Rare Diseases 2014;9:42; Saadoun et al, Arthritis Rheum 2010;62:2806-12). Patients die of vasculitic, gastrointestinal and central nervous system complications. The Committee was not aware of New Zealand-specific prevalence data for different presentations of Behçet's disease.

16. Topical Non-Steroidal Anti-inflammatory Drugs (NSAIDs) for osteoarthritis

Application

- 16.1. The Committee considered a paper from PHARMAC staff regarding the use of topical non-steroidal anti-inflammatory drugs (NSAIDs) for osteoarthritis.

Recommendation

- 16.2. The Committee **recommended** that a topical NSAID be funded for use in osteoarthritis subject to Special Authority criteria for patients for whom alternative oral treatments (oral NSAIDs, paracetamol, tramadol, codeine) are contraindicated, with a low priority. The Committee further **recommended** that advice be sought from the Analgesic Subcommittee of PTAC on the specific NSAID presentation(s) that should be funded and appropriate Special Authority criteria.
- 16.3. 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; (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

- 16.4. The Committee noted that the Rheumatology Subcommittee of PTAC had advised PHARMAC staff in 2011 that, taking into account the financial considerations, the lack of good evidence for topical NSAIDs in osteoarthritis (OA) did not warrant further investigation of funding this class of agents by PHARMAC staff at that time. The Committee noted that the Rheumatology Subcommittee had subsequently (October 2014) recommended that PHARMAC staff seek updated advice on topical NSAIDs for OA.
- 16.5. The Committee noted that OA is the most common form of arthritis, affecting more than 300,000 New Zealanders. The Committee noted that OA is more common in people over the age of 65 years and significantly affects patients' health and wellbeing.
- 16.6. The Committee noted that there is a wide range of funded treatment options for OA, including oral NSAIDs, paracetamol, tramadol, codeine, capsaicin cream and intra-articular corticosteroids; however, options are limited in patients who cannot take oral treatments due to intolerance or contraindication. In particular, the gastrointestinal side effects of oral NSAIDs can be treatment-limiting in older patients, and opiates are often not suitable for older patients. The Committee noted that many patients with hand and/or knee OA who are unable to tolerate oral NSAIDs have significant morbidity.
- 16.7. The Committee noted that topical NSAIDs have a more favourable adverse event profile compared with oral NSAIDs.
- 16.8. The Committee noted that a number of international guidelines now recommend the use of topical NSAIDs in managing hand and/or knee OA, including the European League Against Rheumatism (EULAR), American College of Rheumatology (ACR), National Institute for Health and Care Excellence (NICE) and the American Association of Orthopaedic Surgeons (AAOS).
- 16.9. The Committee noted that the evidence used to inform the international guidelines recommending the use of topical NSAIDs for hand and/or knee OA was generally limited to shorter-term studies in patients under the age of 80 years. The Committee noted that almost all OA trials focus on a single joint, whereas older adults with OA typically suffer from pain in multiple joints. The Committee noted that guidelines appeared to

recommend the use of topical NSAIDs largely because of a favourable adverse event profile compared with oral NSAIDs, with the evidence supporting an initial benefit in reducing symptoms.

16.10. The Committee noted the Lin et al (BMJ 2004;329:324) meta-analysis reviewed by the Rheumatology Subcommittee in 2011, which showed that topical NSAIDs were superior to oral NSAIDs only in the first two weeks of treatment, after which there was no evidence of efficacy benefit over placebo. The Committee noted that randomised controlled trials (RCTs) included in the meta-analysis were of short duration for what is a chronic condition, and considered that there was a need for more evidence from trials lasting longer than four weeks.

16.11. The Committee noted a more recent 2012 Cochrane review of topical NSAIDs for chronic musculoskeletal pain in adults (Derry et al Cochrane Database of Systematic Reviews 2012;Issue 9;CD007400).

- The Committee noted that the authors concluded that topically applied NSAIDs can provide relief of chronic OA pain in the knee or hand that is equivalent to that of oral NSAIDs. The review found no evidence for topical NSAIDs benefitting any other chronic pain conditions, nor for other joints affected by OA, and the availability of high quality evidence overall was limited, particularly for ibuprofen 5% gel.
- The Committee noted that adequate data for the purposes of the Cochrane meta-analysis was only available for topical diclofenac. The number needed to treat (NNT) for at least 50% pain relief or its equivalent during 8-to-12 weeks compared with placebo, was calculated as 6.4 for the solution and 11 for the gel formulation. There were too few data of good quality to calculate NNTs for any other individual topical NSAIDs compared with placebo.
- The Committee noted that direct comparisons of any topical NSAIDs with an oral NSAID formulation did not show any differences in efficacy. There was an increase in local adverse effects (mostly mild skin reactions) with topical NSAIDs compared with placebo or oral NSAIDs, but no increase in serious adverse events and gastrointestinal adverse events were reduced compared with oral NSAIDs. For localised skin reactions compared with placebo, the number-needed-to-harm (NNH) with topical NSAIDs was 16. For adverse events compared with oral NSAIDs, the NNH for topical NSAIDs was 6.4.
- The Committee noted the authors' view that an advantage of topical formulations is that the active component stays close to the site of application, and systemic levels in the blood and more remote tissues remain relatively low. The efficacy appears to be strongly related to the formulation, with dimethylsulfoxide (DMSO)-containing formulations particularly good at enabling tissue penetration. It was noted that DMSO formulations are not currently available in New Zealand.
- The Committee noted that the longest trials examined in the Cochrane review were up to 12 weeks' duration, which the Committee considered is likely insufficient when considering the treatment of chronic conditions like OA.
- The Committee noted that the NNTs for topical diclofenac increased in size as trial length increased: 2-3 weeks (NNT=5.0); 4-6 weeks (NNT=5.2); 8-12 weeks (NNT=10). Members noted that it is uncertain whether this represents a waning of efficacy over time or a regression to the mean due to the natural course of musculoskeletal pain, and considered that longer controlled trials are needed as confirmation.
- The Committee noted that the Cochrane authors highlight the potential for publication bias. Data presented in poster forms at international conferences were

requested of companies, but none felt able to respond. The authors further comment that “although there were over 1000 participants in the 8-12 week pooled analysis for diclofenac, the NNT of 6.4 means that 566 participants in unavailable studies would be needed to raise the NNT to 10, a level often seen as an inadequate response”

- The Committee further noted the large placebo response with topical NSAIDs, approximately 50% in longer duration studies.
- 16.12. The Committee noted two trials by Peniston (Phys Sportsmed. 2011 Sep;39:31-8; Clin Interv Aging. 2012;7:517-23) which provided some reassurance about the safety of diclofenac gel up to 12 months of use.
 - 16.13. Overall, the Committee considered that the available evidence suggests that topical NSAIDs provide a similar effect to oral NSAIDs for short-term treatment of pain from single-joint hand or knee OA, but longer-term safety and efficacy data are lacking, along with evidence for multiple-joint OA. The best studied topical NSAID is topical diclofenac.
 - 16.14. The Committee noted that there are several treatment options currently available for patients with OA who are intolerant or contraindicated to oral NSAIDs. The Committee noted that capsaicin cream 0.025% is an alternative funded treatment option for patients with OA who cannot take any oral treatments; however, members noted that some patients disliked the burning sensation from capsaicin cream.
 - 16.15. The Committee considered that intra-articular corticosteroid injections are also an option for patients who cannot take oral treatments; however, these are really only an option for knee osteoarthritis, and can be painful procedures with small risks of infection and bleeding.
 - 16.16. The Committee noted that buprenorphine patches would provide another treatment option; however, these are not currently funded in New Zealand.
 - 16.17. The Committee considered that the dose of topical NSAIDs would typically be 2 to 4 g of 5% gel four times per day, with length of use depending on whether it was used regularly or to control flares. The Committee considered that patients would use approximately 50-100 g per week, or 200-400 g per month of 5% gel.
 - 16.18. The Committee considered that given the high cost and large potential patient numbers, it would not be financially feasible for PHARMAC to fund topical NSAIDs without restrictions, noting that there were many uses for topical NSAIDs other than OA, such as sports injuries/strains.
 - 16.19. The Committee considered that it would be reasonable to restrict topical NSAIDs to patients with hand or knee OA who cannot take oral NSAIDs due to intolerance or contraindication. However, members noted that this patient pool would still be large (potentially half of elderly people with OA) and the Committee considered that PHARMAC staff should take further advice from the Analgesic Subcommittee on creating tight Special Authority criteria. The Committee considered that specific formulations available in New Zealand should be considered and assessed for suitability.