

PTAC meeting held on 6 & 7 November 2014

(minutes for web publishing)

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

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

PTAC may:

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

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1. Matters Arising / Correspondence

Rivaroxaban

- 1.1. The Committee noted correspondence from Bayer in response to the Committee's May 2014 meeting minutes on rivaroxaban. The Committee maintain its previous recommendations relating to the treatment. The Committee considered that its May 2014 meeting minutes on rivaroxaban adequately reflect the uncertainty when attempting to draw conclusions from indirect comparisons of the different pivotal trials for the three novel oral anticoagulants.

Bart's solution

- 1.2. The Committee noted the correspondence from the New Zealand National Committee of the Australian and New Zealand College of Anaesthetists in response to its August 2014 meeting minutes. The Committee maintained its previous recommendations to not list Bart's solution on the HML.

Ranolazine

- 1.3. The committee noted correspondence from TeArai BioFarma relating to ranolazine for use in patients with refractory angina.
 - 1.3.1. The Committee noted that ranolazine is not yet registered in New Zealand. The Committee invited the submission of a full application for ranolazine to PTAC once the product is registered in New Zealand.

Correspondence from a Respiratory Nurse Practitioner

- 1.4. The Committee noted the correspondence from a Respiratory Nurse Practitioner requesting that PTAC consider extending the applicant criteria to include Nurse Practitioners for the Long Acting Muscarinic Antagonist special authority.
- 1.5. The Committee **recommended** that PHARMAC explore changing the applicant from general practitioner or relevant specialist to 'relevant practitioner' to enable nurse practitioners with 'respiratory scope of scope of practice', to apply for Special Authority approval.

Pertuzumab

- 1.6. The Committee noted correspondence from the Breast Cancer Aotearoa Coalition (BCAC) regarding pertuzumab (Perjeta) for the treatment of metastatic HER2-positive breast cancer. The Committee noted that it had previously recommended pertuzumab be funded with low priority. Members noted that BCAC had provided information regarding an updated overall survival analysis of the pivotal phase III study (Cleopatra) presented recently at the European Society of Medical Oncology Meeting held on 28 September 2014. Members noted the conference abstract provided evidence that pertuzumab plus trastuzumab treatment improved overall median survival by around 15.7 months compared with trastuzumab alone. Members considered this to be an impressive and clinically important result but expressed caution at changing its previous recommendation based on a conference presentation alone. The Committee **recommended** that it review the updated overall survival analysis from the Cleopatra study once it was published and an updated cost effectiveness analysis had been undertaken.

Bevacizumab for ovarian cancer

- 1.7. The Committee noted the correspondence from Roche Products in response to its February 2014 meeting minutes regarding the funding of bevacizumab (Avastin) for the

treatment of advanced epithelial ovarian, fallopian tube or primary peritoneal cancer. The Committee did not consider any of the points raised changed its view and reiterated its previous recommendations.

2. Subcommittee Minutes

Endocrinology Subcommittee Minutes, June 2014

- 2.1. The Committee noted and accepted recommendations in paragraphs 5.4, 5.18, 5.23, 5.32, 5.36, 5.41 and 5.51 of the Endocrinology Subcommittee Minutes held on 17 June 2014.
- 2.1.1. Regarding paragraph 3.4, the Committee did not support the recommendation by the Endocrinology Subcommittee at this time to fund cinacalcet in the HML using the criteria recorded in the Endocrinology Subcommittee Minutes. The Committee considered that cinacalcet should be presented to the Nephrology Subcommittee in December 2014 as a paper before any further recommendation or funding decision is made.
- 2.1.2. The Committee noted, with regards to the Corticosteroids section of the Endocrinology Subcommittee minutes, that it is important that action points are not 'lost' because they are not recommendations in the minutes.
- 2.1.3. The Committee further discussed the recommendation in paragraph 5.36 regarding strontium ranelate. Members noted Medsafe's regulatory concern regarding this drug (stated after the Endocrinology Subcommittee minutes were signed by the Chair). The Committee agreed with the Endocrinology Subcommittee's recommendation to decline the funding application for strontium ranelate.

Reproductive and Sexual Health Subcommittee Minutes, July 2014

- 2.2. The Committee noted and accepted recommendations in paragraphs 4.4, 4.7, 4.11, 4.24, 4.26 and 4.35 of the Reproductive and Sexual Health Subcommittee meeting held on 28 July 2014.
- 2.2.1. Regarding recommendations in paragraphs 3.6, 4.27 and 4.28 relating to the levonorgestrel releasing intrauterine system (LIUS), Mirena, the Committee noted and accepted these recommendations and further recommended that an application be submitted to PTAC for all LIUS (-Mirena) indications.
- 2.2.2. The Committee discussed the recommendation in paragraph 4.3: 'The Subcommittee **recommended** that the opinion of the Dermatology Subcommittee be sought as to what formal documentation is required to confirm a patient has a latex allergy.'
- 2.2.3. Members noted that there are three methods of identifying a latex allergy;
1. RAST/Skincap latex blood test
 2. Patch testing (contact urticaria testing) Skin prick testing.
- 2.2.4. The Committee considered that one or other of these tests should be enough to confirm a latex allergy. The Committee noted that latex allergy is usually a type 1 allergy reaction (as opposed to rubber allergy being a type IV reaction)
- 2.2.5. The Committee considered that the Dermatology Subcommittee view was no longer required to determine tests required to confirm a patient has a latex allergy.

- 2.2.6. The Committee discussed the recommendation in paragraph 4.17, 'to delist combined contraceptives containing desogestrel.' The Committee considered that delisting was unnecessary and it was up to individual clinicians to ensure appropriate prescribing of this pharmaceutical.
- 2.2.7. With regards to the recommendation in paragraph 4.48 and the funding of mefenamic acid, the Committee considered that there was no evidence that a third NSAID would have any benefit for patients with primary dysmenorrhoea, dysfunctional uterine bleeding and pain or menorrhagia due to IUCDs who have received insufficient clinical benefit from prior treatment with either two NSAIDs or one NSAID and an oral contraceptive. Therefore, the Committee did not accept the recommendation from the Reproductive and Sexual Health Subcommittee.
- 2.2.8. The Committee discussed the recommendation in paragraph 6.7 regarding listing a female condom with a medium priority. The Committee noted that the recommendation was in relation to a different model of female condom than in the application previously assessed by PTAC. Members accepted the Subcommittee recommendation but in turn **recommended** that PHARMAC undertake further analysis of the product.

Diabetes Subcommittee, August 2014

- 2.3. Members accepted minutes from the Diabetes Subcommittee meeting held on 2 August, 2014. Members discussed paragraph 6.2 of the Diabetes Subcommittee Minutes and agreed with the Special Authority for the new oral agents and the recommendation for funding with a low priority. Members noted that the priority may change following the outcome of long-term data.

Neurological Subcommittee, August 2014

- 2.4. The Committee reviewed the minutes from the August 2014 Neurological Subcommittee meeting and noted and accepted all items.

Gastrointestinal Subcommittee, May 2014

- 2.5. The Committee noted and accepted the Minutes of the Gastrointestinal Subcommittee meeting held on 21 May 2014.
 - 2.5.1. Regarding item 5.2, the Committee noted the discontinuation of cimetidine, an H2 antagonist. Members considered cimetidine is used for several unique indications for small patient groups and PHARMAC staff should continue to seek an alternative supply if possible.
 - 2.5.2. Regarding item 5.5.3, the Committee did not agree with the recommendation from the Subcommittee to change the priority for adalimumab as rescue therapy for Crohn's disease based on clinical need for this patient group. The Committee considered this application should remain a low priority for funding on the basis of clinical need for this group compared to other funding applications.

3. Dabrafenib for the treatment of BRAF V600 mutation-positive unresectable (Stage III) or metastatic (Stage IV) malignant melanoma

Application

- 3.1. The Committee considered a funding application from GlaxoSmithKline NZ Ltd for the funding of dabrafenib (Tafinlar) for the treatment of BRAF V600 mutation-positive unresectable (Stage III) or metastatic (Stage IV) malignant melanoma.

Recommendation

- 3.2. The Committee **recommended** that the application for dabrafenib for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma be declined.
- 3.3. The Committee considered given the high unmet need for effective treatments for metastatic melanoma it would be appropriate for one of vemurafenib, ipilimumab or dabrafenib to be funded. Members noted that all three treatments had been recommended for decline primarily due to their very poor cost effectiveness at the proposed prices. The Committee considered that all three offered some clinical benefit and **recommended** that PHARMAC run a competitive process to enable one of these treatments to be funded if reasonably cost effective.
- 3.4. The Decision Criteria particularly relevant to this recommendation are (i) *The health needs of all eligible people within New Zealand* (iii) *The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;* (iv) *The clinical benefits and risks of pharmaceuticals;* (v) *The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services;* and (vi) *The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 3.5. The Committee noted that New Zealand has one of the highest melanoma incidence rate in the world and it is the fourth most common cancer in NZ. Members considered that there was a high unmet medical need for new effective treatments for patients with metastatic malignant melanoma. Members noted that they had previously considered applications for two other treatments for metastatic malignant melanoma; ipilimumab (Yervoy) for previously treated unresectable (stage IIIC or stage IV) melanoma and vemurafenib (Zelboraf) BRAF V600 mutation positive unresectable (stage IIIC or stage IV) melanoma, both of which were recommended for decline. Members noted that this application for dabrafenib was for the same population as previously considered for vemurafenib.
- 3.6. The Committee noted that dabrafenib, like vemurafenib, was an oral selective inhibitor of mutated forms of BRAF including V600E, V600K, V600D and V600R. Members noted evidence from an analysis BRAF mutations in 344 New Zealand melanoma patients recently presented at the New Zealand Dermatological Society Inc. Annual Scientific Meeting ((Ryder et al Australasian Journal of Dermatology (2014;55: a1) that indicated 37% prevalence of BRAF mutations, which is lower than reported in Australia and internationally. Members noted that co-administration of dabrafenib and the mitogen activated protein/extracellular signal-regulated kinase (MEK) inhibitor trametinib (Mekinist, GSK) in patients with metastatic melanoma was in development.
- 3.7. The Committee noted that BRAF testing was currently available in NZ but it was not universally used because of the lack of funded treatments and variable public funding of the test.
- 3.8. The Committee considered that the key evidence for dabrafenib came from the BREAK-3 study, a Phase III, open-label, randomised study comparing oral dabrafenib with intravenous dacarbazine (DTIC) in previously untreated patients with BRAF V600E mutation positive advanced (stage III) or metastatic (stage IV) melanoma (Hauschild et al Lancet. 2012;380(9839):358). Members noted 250 patients were randomly assigned (3:1) to receive dabrafenib (150 mg twice daily, orally) (n=187) or dacarbazine (1000 mg/m² intravenously every 3 weeks) (n=63) with treatment continued until disease progression, death, study treatment discontinuation, or withdrawal. Members noted that patients in the dacarbazine group were allowed to cross over to receive dabrafenib after disease progression was confirmed by independent review but that patients who permanently discontinued dacarbazine because of an adverse event, withdrawal of consent, or for any

reason other than progression of disease, were not eligible for crossover. Members noted that 44% of dacarbazine patients crossed over.

- 3.9. The Committee considered that the study was of moderate strength and quality. Members noted that median progression-free survival as assessed by the investigator, the primary endpoint of the study, was improved in the dabrafenib group (5.1 months compared with 2.7 months for the dacarbazine group, HR 0.30 (95% CI 0.18–0.51; $p < 0.0001$)). Median progression-free survival as assessed by an independent review committee (IRC) was 6.7 months for dabrafenib versus 2.9 months for dacarbazine (HR 0.35; 95% CI 0.20–0.61). Members noted that objective responses, as assessed by the IRC, were seen in 93 (50%) of patients treated with dabrafenib, with six cases (3%) achieving complete response, with median time to response of 6.3 weeks and median duration of response of 5.5 months. Members noted that for patients treated with dacarbazine there were four partial responses in 63 cases, an overall response rate of 6%.
- 3.10. The Committee noted that overall survival data in the Hauschild et al 2012 publication were not mature. Members noted an unpublished update on overall survival presented by Hauschild et al, at the European Society of Medical Oncology (ESMO) conference 2014 (abstract 5785) that indicated after median follow-up of 16.9 months Median Overall Survival in the dabrafenib arm of 20.0 months compared with 15.6 months in the dacarbazine arm. Members note that this result was not statistically significant and confounded due to the extent of crossover. Members noted that the supplier had attempted to model OS rates using Rank Preserving Structure Failure Models and Iterative Parameter Estimation methods. Members considered that the results of these suffered considerable uncertainty due to the trial design and the statistical assumptions used.
- 3.11. The Committee noted that the most common (\geq grade 2) adverse events associated with dabrafenib treatment were skin malignancies (12/187 patients experiencing keratoacanthoma/Squamous cell carcinoma, 4 Basal cell carcinoma and 2 new primary malignant melanomas, 2 of which were attributed to dabrafenib by the investigator), fever (11%), fatigue (6%), arthralgia (5%) and headache (5%) with Grade 3-4 adverse events uncommon with both treatments.
- 3.12. The Committee noted Quality of Life data from BREAK-3, published by Grob et al. (Annals of Oncology 25: 1428–1436, 2014) demonstrated no clinical or statistical improvement for dabrafenib over dacarbazine in global health, measured using the EORTC QLQ-C30 questionnaire, at 6 or 12 weeks. However, members noted improvements in emotional functioning and symptoms of nausea and vomiting, dyspnea and appetite loss.
- 3.13. Overall the Committee considered that the evidence provided demonstrated that dabrafenib improved progression free survival compared with dacarbazine by around 2.4 months. Members considered that the supplier had overestimated overall survival (OS) gain for dabrafenib; members considered likely OS gain lay in the region of 3-6 months. Members considered that these results were similar to vemurafenib and ipilimumab.
- 3.14. The Committee noted that the HR and absolute PFS gain used in the suppliers cost effectiveness model were from an update of BREAK-3 that was presented at ESMO 2014 which were different to the published data, members also considered that the supplier had overestimated OS gain. Members considered that published data for PFS gain should be used and noted that OS data was confounded; members noted that the CUA model was highly sensitive to OS. Members considered that this degree of uncertainty was not acceptable given the high cost per QALY.

4. Aminolevulinic acid hydrochloride for visualisation of gliomas

Application

- 4.1. The Committee considered a funding application from a clinician for the funding of 5-aminolevulinic acid hydrochloride (Gliolan) for visualisation of malignant tissue during surgery for malignant glioma.

Recommendation

- 4.2. The Committee **recommended** that 5-aminolevulinic acid hydrochloride (Gliolan) should be funded in DHB Hospitals for visualisation of malignant tissue during surgery for malignant glioma. The Committee gave this recommendation a high priority.
- 4.3. The Decision Criteria particularly relevant to this recommendation are *(i) The health needs of all eligible people within New Zealand (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 4.4. The Committee noted that approximately 260 patients are diagnosed with primary brain cancer each year in New Zealand around 80% of which would be diagnosed with glioma. Members noted that high grade primary brain cancers are not curable and treatment is aimed at reducing symptoms and prolonging disease free progression and extending survival. Members noted that current treatment comprises debulking surgery, where possible, combined with adjuvant radiation and temozolomide.
- 4.5. The Committee noted that 5-aminolevulinic acid (5-ALA) was a precursor of heme (prosthetic group of haemoglobin, myoglobin, and the cytochromes) that results in accumulation of porphyrins within malignant glioma tissue. In response to blue light these porphyrins strongly fluorescent and can be visualised with a specific filter attachment on a standard neurosurgical microscope. Normal brain tissue reflects the violet-blue light and appears blue, solid tumour tissue reflects as intense (solid) red fluorescence infiltrating tumour cells appears as vague pink fluorescence.
- 4.6. The Committee reviewed evidence from a number of studies examining the effect of 5-ALA on resection rates and residual tumour volume, and evidence examining the effect of surgical success on clinical outcomes.
- 4.7. The Committee reviewed evidence from a randomised Phase III study in patients with suspected malignant glioma contrast enhancing tumour amenable to complete resection (Stummer et al. Lancet Oncol 2006; 7:392-401). Patients were randomised to receive either 20mg/kg of 5-ALA and fluorescence-guided resection (N=161), or conventional microsurgery with white light (n=161). The primary endpoint of the study was the number of patients without contrast enhancing tumour on early MRI (72 hours post-surgery) and 6-month progression free survival assessed by MRI. Members noted that fewer patients with 5-ALA fluorescence-guided surgery had residual tumour visible on early MRI (65% vs 36%, difference of 29%, 95% CI 17-40, p=0.0001) and PFS at 6 months was improved (41.0% vs 21.1%, difference of 19.9% with 95% CI of 9.1-30.7, p=0.0003). Members also noted that 5-ALA also reduced risk of death or progression (hazard ratio 0.73, 95% CI 0.57-0.94, p=0.01) and a reduced median tumour volume (0.0 vs 0.7 cm³, p<0.0001).

However, members noted an influence of age was observed on the degree of resection which confounded these results. Members noted that there was no difference in the frequency or severity of adverse events within 7 days of surgery and at 6 weeks post-surgery median Karnofsky performance status score was 90 for both groups.

- 4.8. The Committee reviewed evidence from a reanalysis of patients enrolled in the Stummer 2006 study (Pichlmeier et al Neuro-Oncology 10, 1025–1034, 2008). This study evaluated whether the Radiation Therapy Oncology Group recursive partitioning analysis (RTOG-RPA) would predict survival of these patients and whether there was any benefit from extensive resections depending on RPA class. Members noted that patients were allocated into RTOG-RPA classes III–V based on age, KPS, neurological condition, and mental status (as derived from the NIH Stroke Scale). Members noted that RPA class predicted overall survival; RPA classes III, IV, and V was 17.8, 14.7, and 10.7 months, respectively, with 2-year survival rates of 26%, 12%, and 7% ($p < 0.0007$).
- 4.9. The Committee reviewed evidence from a prospective, non-interventional multicenter cohort study examining correlation between residual tumour size and outcomes in 180 patients with histological diagnosis of glioblastoma, small enhancing or no residual tumour on post-operative MRI, and intended temozolomide radiochemotherapy. Members noted that the prognostic value of O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation was investigated in a subgroup of patients. Members noted that median survival was 16.9 months in patients with residual tumour diameters >0 to ≤ 1.5 cm (95% CI: 13.3-20.5, $p = 0.039$), and 13.9 months (10.3-17.5, overall $p < 0.001$) in with residual tumour diameters >1.5 cm. Members noted that patient age at diagnosis and extent of resection were independently associated with survival and that patients with MGMT promoter methylated tumours and complete resection had the best prognosis.
- 4.10. The Committee considered that overall the evidence demonstrated that the use of 5-ALA improved resection rates and extent of tumour resection and considered that this would likely be associated with improved progression free survival and overall survival.
- 4.11. The Committee noted that 5-ALA required use of a neurosurgical microscope with a filter attachment that cost around \$90,000. Members noted that currently 6 DHBs have Neurosurgical units, 3 of which already had this equipment and 1 was planning on upgrading their equipment to include the filter shortly.
- 4.12. The Committee considered that the funding of 5-ALA would not increase the overall number of patients undergoing neurosurgery for glioblastoma, however, members considered that duration of neurosurgical procedures and theatre time may be increased as surgeons would be more motivated to attempt complete resection. Members considered that there was a risk of more comorbidity from more aggressive surgery but this may be countered by surgery being more accurate.

5. Fampridine for improvement of walking ability in multiple sclerosis

Application

- 5.1. The Committee considered a funding application from Biogen Idec for fampridine (Fampyra) for the symptomatic improvement of walking ability in patients with multiple sclerosis (MS).

Recommendation

- 5.2. The Committee **recommended** that the application for fampridine for the symptomatic improvement of walking ability in patients with multiple sclerosis be declined, but noted that the Committee would consider reviewing this recommendation should new long term data regarding efficacy become available.

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

Discussion

- 5.4. The Committee noted the supplier had proposed restricting funding to patients who have a diagnosis of clinically definite multiple sclerosis, are not receiving any MS disease modifying treatment, have an impaired walking ability as demonstrated by an EDSS (Expanded Disability Status Scale) score of 4.0 to 7.5 inclusive, and demonstrate an adequate improvement - at least a 6-point improvement in the MSWS-12 score (Multiple Sclerosis Walking Scale) during an 8 week initiation trial.
- 5.5. The Committee noted that fampridine is a non-selective potassium channel blocker and is a lipid-soluble drug that readily crosses the blood brain barrier.
- 5.6. The Committee noted that fampridine is an oral tablet taken twice daily and is indicated for all forms of MS.
- 5.7. The Committee noted that fampridine is eliminated through the kidneys unchanged and is not recommended for patients with moderate to severe renal impairment (<50 ml/min).
- 5.8. The Committee considered and reviewed all evidence provided by the supplier.
- 5.9. The Committee considered a phase II, multicentre, randomised, double-blind, placebo controlled, parallel group, study investigating the safety, tolerability and activity of fampridine in patients with MS (MS-F202, Goodman et al. Neurology. 2008;71:1134-1141). 206 patients were randomised to one of four treatment arms with fampridine (10 mg, 15 mg, 20 mg twice daily), or placebo, for 15 weeks. Patients were eligible for inclusion if they had a diagnosis of MS according to McDonald 2001 criteria, were aged 18 to 70 years and were able to complete two trials of the Timed 25 Foot Walk Test (T25FWT) in an average of 8 to 60 seconds. No significant differences were reported between the treatment groups with respect to baseline demographics and disease characteristics. The mean age of patients included in the trial was 49.8 years. Slightly more than half of patients (52.4%) had a diagnosis of secondary progressive MS with the remaining almost equally divided between relapsing-remitting MS (22.8%) and primary progressive (24.8%). The mean duration of disease was 12.0 years. The Committee noted that although the mean EDSS score was 5.8, the range of scores was 2.5-6.5 with a number of patients having lower levels of baseline disability than those proposed in the submission restriction criteria. Furthermore, 38.8% of patients were also prescribed interferon while participating in the study. The primary outcome was percentage change in walking speed measured by the T25FWT at multiple time points during the trial. A 20% improvement in T25FW speed was considered clinically significant. No statistically significant differences were reported between any fampridine arm and the placebo arm. Fampridine was generally well tolerated. Severe and serious adverse events were more frequent at the highest dose.
- 5.10. The Committee considered a phase III, multicentre, double-blind, randomised controlled trial investigating efficacy and safety of fampridine in people with MS (MS-F203, Goodman et al. Neurology. 2009;373:732-38). 301 patients with any type of MS were randomly assigned to receive fampridine 10 mg twice daily or placebo in a 3:1 ratio, for a 14 week treatment period. Eligible patients were aged 18 to 70 years, with clinically definite MS and able to complete two trials of the T25FWT in an average time of 8 to 45 seconds. Treatment groups were reported to be comparable for baseline demographics

and disease characteristics. The age of patients included in the trial ranged from 26-70 years and baseline EDSS scores ranged from 2.5-7.0, with greater than 50% of participants concomitantly taking an immunomodulator treatment. The primary outcome was responder status, defined as a faster walking speed in three of the four visits during treatment, according to the T25FWT. The Committee considered this not to be a clinically relevant outcome variable. Patients were allowed to use an assistive aid as long as it was consistently used at each visit. The authors reported a significantly greater proportion of patients taking fampridine experienced a consistent improvement (>0%) in walking speed compared with placebo (78/224 (35%) vs 6/72 (8%); $p < 0.0001$, odds ratio 4.75, 95% CI 2.1 to 10.9). The Committee considered that an improvement in walking speed of less than 20% was not a clinically relevant outcome. The effect was maintained throughout the 14 week treatment period – mean changes in walking speed at the end of the 14 week period were 0.1 ft/sec for placebo, 0.16ft/sec for fampridine non-responders, and 0.51 ft/sec for fampridine responders. Responders were reported to have improved their walking speed (25.2% vs 4.7%) over placebo as well as their MSWS-12 score (-6.84 vs +0.05). Non-responders showed no gains over placebo. Insomnia, fatigue, back pain and balance disorder were reported more frequently in the fampridine-treated patients compared with the placebo group.

- 5.11. The Committee considered a phase III, multicentre, double-blind, randomised controlled trial investigating the efficacy and safety of fampridine in MS (MS-F204, Goodman et al. *Ann Neurol.* 2010;68:494-502). 239 patients with MS were randomised to fampridine 10 mg twice daily or placebo for a 9 week treatment period. The primary outcome was responder status, with the same definition as in MS-F203. The secondary outcome was the change from baseline in the LEMMT score. The authors reported a statistically significant higher proportion of responders in the fampridine group (42.9% vs 9.3% $p < 0.0001$, odds ratio 8.14, 95% CI 3.7-17.7). As with the MS-F203, the subgroup of responders was compared with placebo and statistically significant improvements in walking speed and MSWS-12 scores were reported. There was no statistically significant improvement in the LEMMT score in the fampridine responders groups vs placebo ($p < 0.028$), and no significant difference in scores between responders and non-responders.
- 5.12. The Committee considered information provided by the supplier including conference posters on the unpublished ENABLE trial, a phase IV, open-label, observational trial. 833 patients were assigned fampridine for 4 weeks, then responders continued to take fampridine for 44 more weeks. The Committee noted that responder was defined as someone having “any improvement in T25FWT speed at weeks 2 and 4 and any improvement in MSWS at week 4”. Members considered that this responder definition differed from that used in the pivotal trials. Members noted that 84% of patients met the response criteria, responders had an improvement in SF-36 PCS over non-responders (+3.29 vs -1.14), and utility as measured by EQ-5D also improved (0.64 vs 0.60). The Committee considered that a comparison based on a single arm open label observational study did not provide robust evidence to inform an estimate for health gain, the long-term durability of utility score improvements reported in the study was uncertain, and utility score improvements could be biased by a strong placebo effect.
- 5.13. The Committee considered pooled pivotal trial efficacy data provided by the supplier. Members considered that the absolute time to walk 25 feet in the pooled treatment arm for the T25FWT was 10.7 seconds, compared with a time for placebo patients of approximately 11.3 seconds. The Committee considered the clinical relevance of this difference in treatment response to be extremely questionable. Members considered that the change in MSWS-12 scores reported did not reach the minimal clinically important difference, similarly the changes in the LEMMT score and Ashworth scale scores were not likely to be clinically relevant. The Committee considered the absolute treatment effect to be subject to uncertainty. Members considered that the pooled pivotal data did not demonstrate superiority to placebo.
- 5.14. The Committee noted that the highest incidence of adverse reactions identified for the pivotal trials in patients with fampridine related to the nervous system excitation including

insomnia, balance disorders, dizziness, headache and asthenia. The Committee also noted that during post-marketing surveillance there have been reports of seizures.

- 5.15. The Committee considered the evidence to support the use of fampridine for the symptomatic improvement of walking ability in patients with MS to be weak and the quality of the evidence to be moderate.
- 5.16. The Committee considered that the evidence provided did not demonstrate that improved walking speed equates to improved quality of life. Members also considered that evidence correlating walking speed with EDSS scores was not robust and that the relationship between quality of life and improved walking speed was not clearly demonstrated in any of the pivotal trials.
- 5.17. The Committee considered that there were no other treatments listed on the Pharmaceutical Schedule specifically targeting walking improvement once treatment with a disease modifying treatment (DMT) had been stopped. Members considered if fampridine was listed that it would be used alongside exercise training, physiotherapy, and assisted walking aids. Members considered that there may be limited access to exercise training and physiotherapy in DHB public hospitals. Members considered that the proposed restrictions would preclude concomitant use of DMTs, but a significant number of patients in the pivotal trials were on DMTs.
- 5.18. The Committee considered that the pivotal trials focussed on endpoints with respect to walking ability but that cognitive function and fatigue were also relevant MS patient outcomes that were not assessed. Members noted that the T25FWT was only one variable of the Multiple Sclerosis Functional Composite test, which also includes the 9-hole peg test and paced auditory Serial Addition test. Members discussed the appropriateness of using one variable as opposed to all three as an endpoint in clinical trials.
- 5.19. The Committee considered that the proposed continuation criteria should also include an objective measure of walking ability, such as the T25FWT, in addition to the MSWS-12.
- 5.20. The Committee considered that the pivotal trials were of short duration and it was uncertain whether reported improvements in walking ability would be maintained long term. Members noted that NICE, in a report published October 2014, had considered fampridine not to be cost-effective. The Committee noted that there are at least ten fampridine trials in progress, and would be willing to review the results of these trials when published, particularly those relating to long-term benefit and HRQOL.

6. Dimethyl fumarate for relapsing remitting multiple sclerosis

Application

- 6.1. The Committee considered a funding application from Biogen Idec for dimethyl fumarate (Tecfidera, also known as BG-12) for the treatment of patients with relapsing remitting multiple sclerosis (RRMS). The supplier proposed that dimethyl fumarate is listed in Section B of the Pharmaceutical Schedule with the same access criteria as natalizumab and fingolimod.

Recommendation

- 6.2. The Committee **recommended** that dimethyl fumarate be funded with a medium priority, subject to the same access criteria as natalizumab and fingolimod, provided it was no more expensive than the beta-interferons or glatiramer acetate.
- 6.3. The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;*

(iv) The clinical benefits and risks of pharmaceuticals; and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.

Discussion

- 6.4. The Committee noted that dimethyl fumarate is an oral treatment taken twice daily for relapsing remitting multiple sclerosis. The Committee considered that the exact mechanism of action was unknown, but its anti-inflammatory and cytoprotective properties are thought to be mediated through the activation of the nuclear factor (erythroid derived 2)-like 2 transcriptional pathway. The Committee noted that Fumaderm (fumaric acid esters) is used in Germany to treat severe psoriasis.
- 6.5. The Committee considered and reviewed all evidence provided by the supplier and one systematic review, two posters and two quality of life studies identified by PTAC.
- 6.6. The Committee considered the DEFINE trial reported by Gold R et al. (N Engl J Med 2012;367(12):1098-1107), which was a 2 year, randomised, multicentre, double blind, placebo controlled dose comparison study. 1237 patients with RRMS were randomised (in a 1:1:1 ratio) to receive dimethyl fumarate 240 mg twice daily, dimethyl fumarate 240 mg three times daily or placebo. Patients were aged 18 – 55 years old, had an EDSS of 0-5.0, and had a diagnosis of RRMS. The Committee considered that baseline demographics and disease characteristics were generally well balanced and noted that the mean EDSS score on entry was 2.4, with approximately 40% of patients having previously received prior therapy with either natalizumab, an interferon or glatiramer acetate. The Committee noted 27% of the patients in the twice daily dimethyl fumarate group and 26% in the thrice daily dimethyl fumarate group, as compared with 46% in the placebo group, had a relapse at 2 years ($P < 0.001$ for both comparisons), and the hazard ratio (HR) for the risk of relapse with dimethyl fumarate as compared with placebo during the 2 year period was 0.51 for the twice daily group (95% confidence interval [CI], 0.40 to 0.66) and 0.50 for the thrice daily group (95% CI, 0.39 to 0.65) ($P < 0.001$ for both comparisons). The Committee considered the ARR at 2 years was 0.17 in the twice daily dimethyl fumarate group as compared with 0.36 in the placebo group; rate ratio 0.47 (95% CI 0.37 to 0.61), $p < 0.001$. The Committee noted that twice daily dimethyl fumarate reduced the risk of confirmed progression of disability that was sustained for 12 weeks by 38% compared with placebo (HR 0.62 95% CI 0.44-0.87, $p = 0.005$). Members considered that sustained disability progression confirmed for 6 months would provide a more robust indication of the treatment effect given that patients may recover from relapse.
- 6.7. The Committee considered the CONFIRM trial reported by Fox RJ et al. (N Engl J Med 2012; 367(12):1087-1097), which was a 2 year, multicentre, randomised, double-blind, placebo controlled study which contained a rater-blinded reference comparator of glatiramer acetate. 1430 patients with MS were randomly assigned in a 1:1:1:1 ratio to receive oral placebo, dimethyl fumarate 240 mg twice daily, dimethyl fumarate 240 mg thrice daily, or subcutaneous daily injections of 20 mg of glatiramer acetate. The Committee noted that the study was not designed to test the superiority or noninferiority of dimethyl fumarate vs glatiramer acetate. The Committee noted that at 2 years, the annualised relapse rate was significantly lower with twice daily dimethyl fumarate (0.22, 95% CI 0.18-0.28), thrice daily dimethyl fumarate (0.20, 95% CI 0.16-0.25), and glatiramer acetate (0.29, 95% CI 0.23-0.35) than with placebo (0.40, 95% CI 0.33-0.49) (relative reduction for twice daily dimethyl fumarate versus placebo, 44%, $P < 0.001$ and 29% for glatiramer acetate versus placebo $P = 0.01$). The Committee noted that reductions in disability progression with twice daily dimethyl fumarate, thrice daily dimethyl fumarate, and glatiramer acetate versus placebo (21%, 24% and 7% respectively) were not significant. The Committee noted that as compared with placebo, twice daily dimethyl fumarate, thrice daily dimethyl fumarate, and glatiramer acetate significantly reduced the mean number of new or enlarged T2-weighted hyperintense lesions at 2 years by 71%, 73% and 54% respectively (all $P < 0.001$) and new T1-weighted hypointense lesions by 57%, 65% and 41% ($P < 0.001$, $P < 0.001$, and $P = 0.002$, respectively).

- 6.8. The Committee noted that in both the DEFINE and CONFIRM trials, health-related quality of life (HRQoL) was a pre-specified tertiary endpoint. In the DEFINE trial it was reported that a clinically meaningful change of 5 points in the Short Form-36 (SF-36) physical component summary scored during 2 years' treatment significantly favoured dimethyl fumarate over placebo 21.8% improved versus 16.2% placebo OR 1.44 (CI 1.0-2.16, p=0.498) (Kappos et al. *Mult Scler* 2014; 20(2)243-252). Members noted that there was no significant clinically meaningful improvement in the mental component summary score and that there was no statistically significant difference between HRQoL with dimethyl fumarate twice daily dosing and placebo when measured by the EQ-5D instrument (Kappos et al *Mult Scler* 2014; 20(2)243-252). In the CONFIRM trial, HRQOL was reported to be worse in patients with greater disability at baseline and who relapsed during the study, and improved with dimethyl fumarate treatment, although in twice daily dosing no clinically meaningful (>5 points on the Physical Component Summary) significant differences were seen on either the physical or mental component summary scores of SF-36 (Kita et al *Mult Scler* 2014; 20(2) 253-257).
- 6.9. The Committee considered an interim analysis from the 5 year ENDORSE study (Gold et al 2014, Poster 2014 Joint ACTRIMS-ECTRIMS Meeting Sept 10-13 Boston, MA, USA), an open label extension of DEFINE and CONFIRM. Members considered that the treatment effects reported in the CONFIRM and DEFINE trial, with respect to ARR, appeared to be maintained long term, however no formal statistical testing had been performed. Members noted that no additional safety signals had been reported (Pozzilli et al 2014 Poster 2014 Joint ACTRIMS-ECTRIMS Meeting Sept 10-13 Boston MA, USA).
- 6.10. The Committee considered an unpublished indirect comparison, provided by the supplier, of dimethyl fumarate and fingolimod using placebo as a common comparator, which included data from the FREEDOMS, FREEDOMS II, DEFINE and CONFIRM trials. Members considered the supplier's indirect comparison reported an annualised relapse rate that favoured fingolimod but did not reach statistical significance (1.06 [CI 0.83-1.36]) p = 0.6338) and there was no statistical difference between the two treatments in progression of disability (sustained for 3 months).
- 6.11. The Committee considered a systematic review of dimethyl fumarate and other disease modifying therapies and a mixed treatment comparison reported by Hutchinson M et al. (*Curr Med Res Opin* 2014; 30(4):613-27). Members noted that the authors reported in the mixed treatment comparison a 19.2% improvement in ARR with fingolimod compared with dimethyl fumarate but that this was not statistically significant (rate ratio 1.192 [95% CI 0.977-1.4760]). The Committee noted that the authors reported in the mixed treatment comparison that dimethyl fumarate was statistically significantly superior to the interferons, glatiramer acetate, teriflunomide and placebo in reducing ARR, but inferior to natalizumab. Members noted that there was no statistically significant difference between dimethyl fumarate and any of the RRMS treatments with respect to disability progression.
- 6.12. The Committee considered the adverse events that occur more frequently in patients receiving dimethyl fumarate include flushing, gastrointestinal events including diarrhoea, nausea, abdominal pain, and vomiting, nasopharyngitis, proteinuria, and pruritus. Members noted that flushing occurs in about one third of patients treated with dimethyl fumarate.
- 6.13. The Committee considered that although there was good long term safety data from the use of a similar product (fumaric acid esters) in psoriasis there was insufficient long term safety data to comment on the risk of progressive multifocal leukoencephalopathy (PML) with dimethyl fumarate.
- 6.14. Members considered that the quality of the pivotal trials was good, and that the strength of the evidence to support superiority of dimethyl fumarate compared with placebo in reducing ARR was good. The Committee noted that there were no head-to-head comparisons with other disease modifying treatments. Members considered that there was weak to moderate evidence to support non-inferiority of dimethyl fumarate to

fingolimod by way of indirect comparison using placebo as a common comparator. Members considered the mixed treatment comparisons did not demonstrate any significant difference in disability progression when compared indirectly to other DMTs.

- 6.15. With regards to the appropriate treatment comparator the Committee considered that dimethyl fumarate fell between fingolimod and the beta-interferons/glatiramer acetate.
- 6.16. The Committee noted that two new treatments (natalizumab and fingolimod) had recently been funded for RRMS, which included fingolimod being an oral option, and the Committee did not consider there were currently any significant problems with access to these treatments for patients with clinically definite RRMS. Members considered that dimethyl fumarate would provide another first line oral treatment option with a different risk profile to that of fingolimod. The Committee considered dimethyl fumarate may be useful for patients who do not tolerate the other new agents (natalizumab and fingolimod) or if treatment with the new agents would be clinically inappropriate.
- 6.17. The Committee considered that if dimethyl fumarate was available as a first line treatment option that it would likely represent approximately half of the oral treatment market for new patients with potentially a smaller share from natalizumab. Members considered that it would likely displace the use of interferons and glatiramer acetate.
- 6.18. The Committee considered that the minutes from this discussion should be provided to the Neurological Subcommittee for their review at the next Subcommittee meeting.

7. Teriflunomide for multiple sclerosis

Application

- 7.1. The Committee considered a funding application from Sanofi for teriflunomide (Aubagio) for the treatment of patients with relapsing forms of Multiple Sclerosis (MS). The supplier proposed that teriflunomide is listed in the Pharmaceutical Schedule with the same access criteria as applies to natalizumab and fingolimod.

Recommendation

- 7.2. The Committee recommended that teriflunomide be funded with a low priority, subject to the same criteria as applies to natalizumab and fingolimod.
- 7.3. The Decision Criteria particularly relevant to this recommendation are *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; and (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 teriflunomide is an immunomodulatory agent with anti-inflammatory properties and is formulated as a tablet, taken orally once daily. The Committee noted that the parent compound of teriflunomide, leflunomide, is registered for the treatment of rheumatoid arthritis and is fully funded without restriction on its use.
- 7.5. The Committee considered three randomised controlled trials, one long term follow up study and three posters provided by the supplier. In addition, members considered literature not provided by the supplier including systematic reviews with meta-analyses, secondary reports of the first randomised controlled trial, an abstract of a terminated randomised controlled trial, and a study registration of another randomised controlled trial that appeared not to have been published.

- 7.6. The Committee considered the TEMSO trial reported by O'Connor et al. (N Engl J Med 2011;365(14):1293-1303), which was a 108 week, randomised, placebo-controlled trial. 1088 patients with MS were randomised in a 1:1:1 ratio to receive a once-daily oral dose of placebo, 7 mg or 14 mg of teriflunomide for 108 weeks. Patients were required to be aged 18-55 years, have an EDSS score of 5.5 or lower and have had at least two relapses in the previous two years or one relapse during the preceding year. The Committee considered that baseline demographic and disease characteristics across the three groups were similar, noting that patients mostly had relapsing remitting MS, were mostly women, had a mean age of 38 and a mean EDSS of 2.7. The Committee noted that teriflunomide reduced the annualised relapse rate (0.54 for placebo, vs 0.37 for teriflunomide at either 7 mg or 14 mg), with relative risk reductions of 31.2% and 31.5% respectively; (p=0.03). The Committee noted that the proportion of patients with confirmed disability progression was 27.3% with placebo, 21.7% with teriflunomide at 7 mg (p=0.08), and 20.2% with teriflunomide at 14 mg (p=0.03), hazard ratio (HR) for teriflunomide 7 mg versus placebo (HR 0.76, 95% CI 0.56-1.05), and for teriflunomide 14 mg versus placebo (0.70 (0.51-0.97)).
- 7.7. The Committee considered the TOWER trial reported by Confavreux et al. (Lancet Neuro 2014;13: 247-256), which was a multicentre, double-blind placebo-controlled phase III study. 1169 patients with relapsing MS were randomised in a 1:1:1 ratio to receive a once-daily oral dose of placebo, 7 mg or 14 mg teriflunomide. Members noted that at the end of the study (48 weeks after the last patient was included) the annualised relapse rate was higher in patients assigned to placebo (0.50 [95% CI 0.43-0.58]) than in those assigned to teriflunomide 14 mg (0.32 [0.27-0.38]; p=0.0001) or 7 mg (0.39 [0.33-0.46]; p=0.0183). The annualised relapse rate, relative risk for teriflunomide 14 mg was 0.64 (95% CI 0.51-0.79) and 0.78 (95% CI 0.63-0.96) for teriflunomide 7 mg. The Committee noted that compared with placebo, teriflunomide 14 mg reduced the risk of sustained accumulation of disability (hazard ratio [HR] 0.68 [95% CI 0.47-1.00]; log-rank p=0.0442) and teriflunomide 7 mg had no effect on sustained accumulation of disability (HR 0.95 [0.68-1.35]; log rank p=0.7620).
- 7.8. The Committee considered the TENERE trial reported by Vermersch et al. (Mult Scler 2014;20(6):705-16), which was a multicentre, rater-blinded phase III study. 324 patients with relapsing MS were randomised 1:1:1 to receive treatment with teriflunomide 7 mg once daily or 14 mg once daily (double blind) or subcutaneous interferon beta-1a 22 mcg to 44 mcg (open-label) three times per week. The Committee noted that no difference was reported between either dose of teriflunomide and interferon beta-1a on time to failure and that there was no difference in the annualised relapse rate between interferon beta-1a and teriflunomide (0.22 versus 0.26; p=0.6). The Committee noted that the interferon beta-1a annualised relapse rate was lower than anticipated at study onset and that no data on sustained disability was reported.
- 7.9. Members considered that the quality of the pivotal trials were good, the strength of the evidence to support teriflunomide as an agent to reduce relapse rates to be moderate and the strength of the evidence to support a delay of progression of disability to be weak. Members noted that there were no head-to-head trials with fingolimod, natalizumab or dimethyl fumarate. Members considered there to be moderate quality of evidence of no different or worse outcome for annualised relapse risk and no good evidence of a difference in sustained disability for teriflunomide versus beta- interferon.
- 7.10. The Committee noted that two new treatments including an oral option (natalizumab and fingolimod) had recently been funded on the Pharmaceutical Schedule and did not consider there were currently any significant problems accessing MS treatments for Relapsing remitting MS.
- 7.11. The Committee considered the most common adverse events reported with teriflunomide are diarrhoea, nausea, alopecia and increased alanine aminotransferase. Members noted that increased infections, increased blood pressure, peripheral neuropathy, changes in

white blood cell counts and elevated aminotransferase levels were also reported in the clinical trials.

- 7.12. The Committee noted that teriflunomide had a Category X use in pregnancy warning because of high teratogenic potential.
- 7.13. The Committee considered that other health-sector costs that may be associated with teriflunomide could include liver function and blood pressure monitoring/management, management of diarrhoea, nausea and hair loss and the possible need for cholestyramine to enhance clearance of the drug if needed.
- 7.14. The Committee considered that the minutes from this discussion should be provided to the Neurological Subcommittee for their review at the next Subcommittee meeting.

8. Modafinil (Modavigil) for improving attention and sleep in patients with mood disorders, psychoses, drug dependency and attention deficit disorders

Application

- 8.1. The Committee reviewed an application from a clinician to widen funded access to modafinil (Modavigil) tablets to include patients with mood disorders, psychoses, drug dependency and attention deficit disorders, including patients with stimulant dependency, anxiety, compulsive behaviour disorders, schizophrenia and related psychoses, bipolar depression, depression, and shift workers with mood and sleep problems.

Recommendation

- 8.2. The Committee **recommended** that the application to widen access to modafinil to include patients with mood disorders, psychoses, drug dependency and attention deficit disorders be declined.
- 8.3. 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; (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

- 8.4. The Committee noted that modafinil is currently funded subject to Special Authority criteria as a treatment for narcolepsy for patients in whom subsidised stimulants (methylphenidate and dexamphetamine) are not tolerated or are contraindicated.
- 8.5. The Committee noted that the Medsafe registered indications for modafinil are:
 - to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy;
 - to treat excessive sleepiness associated with moderate to severe chronic shift work sleep disorder where non-pharmacological interventions are unsuccessful or inappropriate; and
 - as an adjunct to continuous positive airways pressure (CPAP) in obstructive sleep apnoea/hypopnoea syndrome in order to improve wakefulness.
- 8.6. The Committee noted that the registered indications in Australia and the USA are the same as those in New Zealand, and in the UK modafinil is only registered for use in narcolepsy.
- 8.7. The Committee noted that supporting evidence provided with the application was limited to a 2011 review article on the use of cognitive enhancers in the treatment of substance

abuse (Brady et al. *Pharmacol Biochem Behav* 2011;99:285-294), a 2013 meta-analysis of trials of modafinil augmentation in unipolar and bipolar depression (Goss et al. *J Clin Psychiatry* 2013;74:1101-7) and a 2012 review of modafinil augmentation in schizophrenia (Wittkamp et al. *Ther Adv Psychopharmacol* 2012;2:115-125).

- 8.8. The Committee noted that it appeared the applicant was primarily requesting access to modafinil be widened to include augmentation of antidepressant and antipsychotic treatment.

Depression

- 8.9. The Committee noted a Cochrane review from 2008 that identified three studies of modafinil in depression and concluded that evidence to date does not support the use of modafinil in the treatment of depression. (Candy et al. *Cochrane Database Syst Rev* 2008(2):CD006722).
- 8.10. The Committee noted the more recent paper provided by the applicant (Goss et al. *J Clin Psychiatry* 2013;73:1101-7) offers a review of data from four randomised controlled trials (RCTs) of modafinil in unipolar depression (n=568) and two RCTs in bipolar depression (n=342). All studies were 6 or 8 weeks' duration. It included two of the studies in the Cochrane review but excluded the third (which dealt with 'atypical' depression). The results from modafinil augmentation in both unipolar and bipolar depression were in general agreement, with the exception of a small study in unipolar depression which was strongly positive. Analysed together the results showed a small, statistically significance effect on depression. When the small strongly positive study was excluded from the analysis the result was a small (Hedges g 0.22) positive effect on depression with a confidence interval of the effect size of 0.32 to 0.09 Hedges g. The Committee noted that while this was a statistically detectable effect size, it appeared to be below that required to provide a clinically relevant improvement in depression and fatigue. In estimating the clinical relevance of the effect size, the Committee referred to Fournier et al. *JAMA* 2010 Jan 6;303:47-53 and Lopez-Pina et al. *Int J Clin Health Psychol* 2009;9:143-159.
- 8.11. The Committee noted that the authors of the Goss 2013 review (*J Clin Psychiatry* 2013;74:1101-7) observed that no significant safety effects were found to indicate differences between modafinil and placebo in dropout rates or serious adverse events, although the data for this was not presented. However, members noted that one of the studies (Dunlop et al. *J Clin Psychopharmacol* 2007;27:614-9, n=73) included in this analysis was discontinued early due to two patients in the modafinil group developing new or worsening suicidal ideation.
- 8.12. The Committee noted that there appears to be limited evidence on the effectiveness of modafinil for treatment-resistant depression; however, members noted that the trials were of short duration and considered that reported improvements in depression and fatigue are unlikely to be clinically significant. The Committee also noted that there are many other treatment options available for treatment-resistant depression.

Schizophrenia

- 8.13. The Committee noted that the paper provided by the applicant (Wittkamp et al. *Ther Adv Psychopharmacology* 2012;2:115-125) considered 15 studies of the impact of modafinil or armodafinil (the R enantiomer of racemic modafinil) on fatigue and activity measures and cognitive functioning in patients with schizophrenia. The paper reviews six studies with a duration of 4 weeks or more (total n=211) and five single-dose studies (total n=97). The Committee noted that the studies were typically small and highly variable in terms of inclusion/duration and measurement parameters.
- 8.14. The Committee noted that the only studies noted in the Wittkamp et al 2012 paper (referred to in the previous paragraph) that showed a statically significant positive effect of treatment on fatigue/activity were an open label 4-week study with n=10 participants and a single dose crossover study looking at activity as measured by actigraphy. The single-

dose studies showed significant positive results on cognitive functioning when modafinil was given to patients with schizophrenia taking antipsychotics. However, these results were not reproduced in studies of 4 weeks or more with the exception of the small open label study that also showed positive results for fatigue measurements.

- 8.15. The authors of the Wittkamp et al 2012 paper reported that, overall, modafinil was well tolerated; however, several studies report that modafinil worsened psychosis in some patients. The Committee noted that modafinil has clinically significant pharmacokinetic interactions with clozapine and quetiapine, both of which are frequently used in this patient group.

Substance abuse

- 8.16. The Committee noted that the applicant provided a review article that provides a rationale for the use of modafinil in substance abuse, and discusses a number of studies in patients who are cocaine or methamphetamine-dependent (Brady et al, *Pharmacol Biochem Behav* 2011;99:285-294). Two studies of use in cocaine-dependence gave mixed results that were confounded by differences in baseline cocaine use in one case and concurrent alcohol abuse in the other. A post-hoc analysis suggested that modafinil, in combination with individual behavioural therapy, was effective in increasing cocaine non-use days in participants without co-morbid alcohol dependence, and in reducing cocaine craving.
- 8.17. The Committee noted that the review article provided (Brady et al, 2011) and a Cochrane review of psychostimulants for treatment of amphetamine abuse (Perez-Mana et al. *Cochrane Database Syst Rev* 2013;9:CD009695) provided no positive results for utility of modafinil in this setting.

Anxiety

- 8.18. The Committee noted that the applicant provided no evidence in support of the use of modafinil in anxiety. The Committee noted that onset or worsening of anxiety is reported as a side effect in a number of studies where modafinil is given for a different indication. The Committee noted a review by Hofmann et al (*Pharmacol Biochem Behav* 2011;99:275-84) which discusses the mixed and seemingly dose-dependent anxiety response-to modafinil treatment in healthy and clinical populations and concludes that the current data suggests it is associated with increased anxiety.

Compulsive behaviour (e.g. gambling)

- 8.19. The Committee noted that the applicant did not provide any supportive evidence for this indication and, in the absence of a defined patient group, the Committee elected not to consider the use of modafinil this indication.

Mood and sleep problems in shift workers

- 8.20. The Committee noted that treatment of excessive daytime sleepiness associated with chronic shift work sleep disorder is a registered indication of modafinil, and there is a reasonable body of evidence available for the use of modafinil in this indication. The Committee noted that a recent Cochrane review (Liira et al. *Cochrane Database Syst Rev* 2014;8:CD009776) concluded that both modafinil and armodafinil increase alertness and reduce sleepiness to some extent in employees who suffer from shift work sleep disorder but they are associated with adverse events.
- 8.21. The Committee noted that Medsafe-registered indication does not include mood disorders associated with shift work. The Committee considered that as “shift workers” is a large population and modafinil is an expensive drug with abuse potential and significant (although rare) side effects, it would be important for the applicant to provide a tight description of the subpopulation likely to benefit the most and provide evidence to support this in order for the Committee to consider this further.

Safety

- 8.22. The Committee noted that common side effects observed in clinical trials of modafinil are relatively mild and include headache, nausea, nervousness, anxiety, rhinitis, back pain and dizziness. However, the Committee noted that there is also the risk of serious adverse events and that the Medsafe datasheet was updated in 2012 to include more information about the risk of serious multiorgan hypersensitivity reactions, serious skin reactions, psychiatric disorders, cardiovascular disease and the potential for dependence.
- 8.23. The Committee noted that modafinil is not approved for paediatric use for any indication due to reports of serious adverse events in the paediatric population.

Overall conclusion

- 8.24. The Committee noted that all the requested indications were off-label, and that modafinil was relatively expensive with a significant abuse and addiction potential. The Committee also noted that modafinil is associated with side-effects, some of which are severe. The Committee considered that insufficient evidence had been provided to support a positive recommendation in any of the requested indications. The Committee noted that it would be pleased to reconsider modafinil in these indications if the applicant could provide a stronger case, with a carefully defined patient groups and supporting evidence in the form of clinical trials (rather than review articles).

9. Aripiprazole (Abilify) for severe irritability in patients with an autism spectrum disorder

Application

- 9.1. The Committee reviewed an application from a clinician to widen funded access to aripiprazole (Abilify) tablets to include the treatment of severe irritability associated with an autism spectrum disorder (ASD) in patients where risperidone has been trialled and discontinued.

Recommendation

- 9.2. The Committee **recommended** that funded access to aripiprazole (Abilify) be widened to include the last-line treatment of severe irritability associated with an autism spectrum disorder (ASD) subject to the following Special Authority criteria, with a high priority:

Initial application – (Autism spectrum disorder*) only from a psychiatrist or paediatrician. Approvals valid for 12 months for applications meeting the following criteria:

All of the following:

- 1 The patient has been diagnosed with an autism spectrum disorder* and has symptoms of severe irritability; and
- 2 An effective dose of risperidone has been trialled and has been discontinued because of unacceptable side effects or inadequate response; and
- 3 The patient is aged less than 18 years.

Renewal application – (Autism spectrum disorder*) only from a psychiatrist or paediatrician or medical practitioner on the recommendation of a psychiatrist or paediatrician. Approvals valid for 2 years for applications meeting the following criteria:

Both:

- 1 The patient is aged less than 18 years; and
- 2 The treatment remains appropriate and the patient is benefiting from treatment.

Note: Indications marked with * are Unapproved Indications

- 9.3. 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; (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

- 9.4. The Committee noted that aripiprazole is currently funded subject to Special Authority criteria as a treatment for schizophrenia and related psychoses for patients in whom risperidone or quetiapine has been trialled and discontinued due to unacceptable side effects or inadequate response.
- 9.5. The Committee noted that the Medsafe registered indications for aripiprazole are:
- the treatment of schizophrenia including maintenance of clinical improvement during continuation therapy;
 - acute and maintenance treatment of manic and mixed episodes with bipolar I disorder with or without psychotic features; and
 - an adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with bipolar I disorder with or without psychotic features.
- 9.6. The Committee noted that in the USA, aripiprazole has recently become indicated for use in irritability associated with autistic disorder, based on two 8-week trials in paediatric patients (aged 6-17 years). The US-recommended dosing schedule is 5–10 mg/day (initial dose 2 mg/day and maximum dose 15 mg/day).
- 9.7. The Committee noted that the applicant provided two 8-week, multicentre, placebo-controlled, double-blind, randomised controlled-trials in children and adolescents (aged 6-17) with autistic disorder and irritability behaviours. The Committee noted that these were the same trials used to support the indication in the US.
- 9.8. In the first trial (Marcus et al, J Am Acad Child Adolesc Psychiatry 2009;48:1110-9), 218 patients aged 6–17 years (mean age 9.7 years) with autistic disorder and with behaviours such as tantrums, aggression and self-injurious behaviour were randomised 1:1:1:1 to aripiprazole (5, 10 or 15 mg/day) or placebo. The primary outcome measure was the caregiver-rated Aberrant Behaviour Checklist Irritability (ABC-I) subscale Other outcome measures were the clinician-rated Clinical Global Impressions-Improvement (CGI-I) score, 'response rate' (proportion of patients with 25% or greater reduction from baseline in ABC-I and CGI-I ≤ 2), safety and tolerability. ABC-I score at baseline was 28-29.
- At 8 weeks, all aripiprazole doses produced significantly greater improvement than placebo in mean ABC-I subscale scores (placebo -8.4; aripiprazole 5 mg/day, -12.4, $p=.032$; aripiprazole 10 mg/day, -13.2, $p=.008$; aripiprazole 15 mg/day, -14.4, $p=.001$) and in mean CGI-I score (placebo 3.3, aripiprazole 5 mg/day, 2.6, $p=.003$; aripiprazole 10 mg/day, 2.5, $p <.001$; and aripiprazole 15 mg/day, 2.5, $p<.001$). At week 8, response rate was significantly greater with aripiprazole 5 mg/day than the placebo (55.8% vs 34.7%; $p=.034$); response rates with aripiprazole 10 mg/day and 15 mg/day were not statistically different from placebo. The Committee noted the high placebo response rate.
 - Aripiprazole was generally well tolerated in the study. Completion rates were high (73% of placebo patients and 83%-87% of aripiprazole patients) and discontinuations due to adverse events were low. The most commonly reported adverse events associated with aripiprazole treatment were sedation, extrapyramidal side effects and weight gain. All aripiprazole doses were associated with significant decreases in serum prolactin. The Committee noted that nearly 1/3 of patients in the aripiprazole 5 mg/day and 15 mg/day groups gained $\geq 7\%$ of body weight, compared with approximately 8% and 15% of patients in the placebo and aripiprazole 10 mg/kg groups, respectively.

- 9.9. In the second trial, from the same study group, (Owen et al, Paediatrics 2009;124:1533-40), 98 patients aged 6–17 years (mean age 9.3 years) with autistic disorder and exhibiting behaviours such as tantrums, aggression and self-injurious behaviour, were randomised to receive placebo or aripiprazole. Aripiprazole was flexibly dosed: initiated at 2 mg/day, with a target dosage of 5, 10, or 15 mg/day (maximum dosage: 15 mg/day), doses were reviewed each week up to six weeks and increased as required. Efficacy outcome measures included ABC-I and CGI-I, response rate' (proportion of patients with 25% or greater reduction from baseline in ABC-I and CGI-I ≤ 2), and safety and tolerability. ABC-I at baseline was 29-30.
- At week 8 there was a significantly greater reduction in ABC-I in the aripiprazole group compared with placebo (-12.9 vs -5.0, respectively, $p < .001$). Similarly, aripiprazole showed significantly greater improvements in mean CGI-I scores compared with placebo at week 8 (2.2 vs 3.6, $p < .001$). Response rate was significantly higher in the aripiprazole group compared with placebo at week 8 (52.2% vs 14.3%; $p < .001$). Discontinuation rates as a result of adverse events were higher for aripiprazole (10.6% vs 5.9% for placebo) as were extrapyramidal symptom-related adverse event rates (14.9% vs 8%) for placebo. Mean weight gain was 2.0 kg on aripiprazole and 0.8 kg on placebo at week 8.
- 9.10. The Committee noted a Cochrane review of aripiprazole in ASD (Ching et al. Cochrane Database Syst Rev 2012;5:CD009043) which performed a meta-analysis of the two trials outlined above. The authors concluded that the evidence suggests that aripiprazole can be effective in treating some behavioural aspects of ASD in children (including irritability, hyperactivity, and repetitive, purposeless actions) but that notable side effects such as weight gain, sedation, drooling, and tremor must be considered.
- 9.11. The Committee considered that the two trials provided moderate strength and quality evidence of benefit of aripiprazole for irritability in ASD. The Committee noted that the patient numbers in the studies were relatively low and the trial durations were relatively short. The Committee considered that longer-term trials were needed given that ASD is a long-term condition.
- 9.12. The Committee considered that the current funded 'last-line' treatment option for this patient group is risperidone, which is indicated for use in ASD in children and adolescents and is typically used at doses of between 1 and 3 mg per day. The Committee considered that, given risperidone is a potent antipsychotic, it was likely that risperidone would be reserved for use in patients only after they had trialled all other alternative treatment options, meaning that in patients who had tried and discontinued risperidone due to adverse effects or lack of efficacy there are currently no alternative funded treatment options. As such, the Committee considered that there was a significant unmet health need in this patient population.
- 9.13. The Committee noted a small ($n=11$) open-label 8-week study of low-dose quetiapine (122.7 ± 39.5 mg/day (range, 50-150 mg/day) in patients with ASD and aggressive behaviour which showed a reduction in aggressive behaviour with quetiapine (Golubchik et al, Clin Neuropharmacol. 2011;34:216-9). The Committee considered that this evidence was not strong enough to support the use of quetiapine in this indication and that more robust trials were needed. The Committee considered that there appeared to be no quality evidence available to support the use of any antipsychotic agent other than risperidone and aripiprazole in this indication at present.
- 9.14. Similarly, the Committee considered that there did not appear to be any quality evidence in support of selective serotonin reuptake inhibitor (SSRI) antidepressants for ASD, noting a Cochrane review which concluded that there is no evidence of effect of SSRIs in children and emerging evidence of harm (Williams et al, Cochrane Database Syst Rev 2013;8:CD004677).

- 9.15. The Committee considered that, if funded, aripiprazole would likely be used as monotherapy in this indication, with other medications such as methylphenidate added as needed in complex cases. The Committee considered that the use of aripiprazole in this setting would be unlikely to reduce the use of any other funded pharmaceutical, with the possible exception of risperidone where patients are currently persisting with risperidone despite suboptimal response.
- 9.16. The Committee considered that aripiprazole may offer some advantages over risperidone in terms of its side effect profile, in particular less weight gain and less prolactin increase; however, the Committee noted that aripiprazole does cause weight gain and has other risks such as extrapyramidal side effects and other adverse effects noted in the clinical trials. Members were uncertain about the clinical implications of prolactin reduction in this group of young people.
- 9.17. The Committee noted that there appears to be no quality evidence to support the use of aripiprazole in disorders such as attention deficit hyperactivity disorder (ADHD) or intellectual disabilities.
- 9.18. Similarly, the Committee noted that there did not appear to be any quality evidence supporting the use of aripiprazole (or any other antipsychotic) in patients with ASD aged 18 and over. For this reason, and taking into account the high cost of aripiprazole compared with other antipsychotics (all of which are fully funded without restrictions with a no better or worse evidence base in adult patients), the Committee did not support the funding of aripiprazole in patients with ASD aged 18 and over.
- 9.19. The Committee considered that the use of aripiprazole for children and adolescents with ASD and irritability would be unlikely to create any significant changes in health-sector expenditure other than for direct treatment costs.
- 9.20. For the purposes of PHARMAC's budget impact analyses the Committee considered that an estimate of approximately 80 patients per year was reasonable.
- 9.21. For the purposes of PHARMAC's cost-utility analyses, the Committee considered:
- the comparator of "no pharmaceutical treatment" was appropriate;
 - the patient population was likely to be more impaired than patients with moderate-to-severe ADHD. The Committee noted that this patient group was severely dysfunctional and frequently required respite care. The Committee considered that PHARMAC's estimate of a quality adjusted life year (QALY) baseline of 0.7 is likely too conservative and should be lower given the level of dysfunction experienced by this patient group;
 - the key trials from which to determine response rates are the two trials described above (Marcus et al, 2009 and Owens et al, 2009). The Committee considered that even in responders there would likely be residual symptoms, but reduced in severity/frequency; and
 - patients would likely require long-term treatment to maintain benefit from aripiprazole. The Committee noted that it would be good clinical practice to regularly review the patient and trial discontinuation.
- 9.22. The Committee considered that, if access to aripiprazole was widened for the requested indication, it would be important to have access to a 5 mg strength if the 10 mg is not scored, but it would not be essential to have access to a 2 mg strength (as few patients are likely to respond to 2 mg). The Committee noted that there would likely be a demand for oral liquid, if access was widened.

10. Rotigotine transdermal patch for the treatment of Parkinson's disease

Application

- 10.1. The Committee considered a funding application from UCB Australia for rotigotine transdermal patches (Neupro) for the treatment of Parkinson's disease.

Recommendations

- 10.2. The Committee **recommended** that rotigotine be listed in Section B and Section H of the Pharmaceutical Schedule for the treatment of Parkinson's disease only if cost-neutral to ropinirole or pramipexole.
- 10.3. 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; (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

- 10.4. The Committee noted that rotigotine is a non-ergot dopamine agonist for the treatment of Parkinson's disease. Members noted that rotigotine transdermal patch is formulated to be applied once daily and is replaced each day with a new patch at a different site of application. The Committee considered that steady state concentrations are achieved over two days, and the absolute bioavailability after transdermal application is approximately 37%, with differences in bioavailability depending on the site of application.
- 10.5. The Committee considered that dopamine receptor agonists are usually considered second line agents after levodopa which is well-established as the most effective agent for the symptomatic treatment of Parkinson's disease. Members considered that use of ergot derivatives including cabergoline, bromocriptine, lisuride and pergolide had diminished due to the potential for causing cardiac valvulopathy.
- 10.6. The Committee considered and reviewed all evidence provided by the supplier.
- 10.7. The Committee considered a long term study of 149 Parkinson's patients in Australia, reported by Hely et al. (Mov Disord 2005; 20(2):190-9) that at fifteen year follow up there was no difference in outcomes for motor complications and mortality for patients whose treatment was initiated with either dopamine agonists or levodopa.
- 10.8. The Committee considered the SP513 trial reported by Giladi et al (Mov Disord 2007; 22(16): 2398-2404), which was a multicentre, double-blind randomized controlled trial investigating the efficacy and safety of rotigotine patches in subjects with early-stage Parkinson's disease. 561 patients were randomised to rotigotine, ropinirole, or placebo. Exclusion therapy included prior therapy with levodopa. Members noted the study reported that in the rotigotine treated group 52% of patients demonstrated a response to treatment (defined as a 20% or greater decrease in the Unified Parkinson's Disease Rating Scale (UPDRS) compared with 68% in the ropinirole treated group and 30% in the placebo group and both the rotigotine and ropinirole treatment groups were considered significant compared with placebo ($P < 0.0001$). The Committee noted that the mean decrease in UPDRS subtotal score was $-7.2 (\pm 9.9 \text{ SD})$ in the rotigotine treatment group compared with $-2.2 (\pm 10.2 \text{ SD})$ in the placebo group ($p < 0.0001$) and $-11.0 (\pm 10.5 \text{ SD})$ in the ropinirole treated group ($p < 0.0001$). Members considered that transdermal rotigotine at doses of $\leq 8 \text{ mg}/24\text{h}$ did not show non-inferiority to ropinirole at doses $\leq 24 \text{ mg}/\text{day}$, and the study was not powered to show superiority. The Committee noted that the adverse events that occurred more frequently among patients assigned to active treatment with rotigotine transdermal patch than patients receiving placebo included application site reactions (38% rotigotine group, 11% placebo, 7% ropinirole), nausea (29% rotigotine

group, 16% placebo, 36% ropinirole), vomiting (12% rotigotine group, 3% placebo 11% ropinirole), somnolence (28% ropinirole group, 20% placebo, 23% ropinirole), dizziness (14% rotigotine group, 10% placebo, 17% ropinirole), and headache (10% rotigotine group, 8% placebo, 9% ropinirole).

- 10.9. The Committee considered the SP515 (CLEOPATRA-PD) trial reported by Poewe WH et al. (Lancet Neurol 2007; 6:513-20), which was a multicentre, double-blind, double dummy, placebo and pramipexole controlled, trial investigating the efficacy and safety of rotigotine in advanced Parkinson's Disease. 204 patients were randomly assigned to receive rotigotine, 201 to receive pramipexole and 101 to receive placebo. All patients were required to be taking a stable dose of levodopa. The Committee noted the mean change in daily off time (as assessed by patient diaries) was -1.58 hours (95% CI -2.27 to -0.90; $p < 0.0001$) for rotigotine compared with placebo and -1.94 hours (95% CI -2.63 to -1.25; $p < 0.0001$) for pramipexole compared with placebo. Members noted that in the rotigotine treated group 59.7% of patients demonstrated a response to treatment (defined as patients with 30% or more reduction in absolute 'off'¹ time) compared with 67% in the pramipexole treated group and 35% in the placebo group; both the rotigotine and pramipexole treatment groups were considered significant compared with placebo ($p < 0.0001$). Members considered that rotigotine and pramipexole showed similar efficacy in all secondary parameters, including time spent "on"¹ without troublesome dyskinesias, number of 'off'¹ periods, motor status after morning wake-up ('on'¹ with or without troublesome dyskinesias or "off"¹), UPDRS II and III scores during on periods and changes in the Parkinson's disease sleep scale. Members considered the adverse events were similar to those reported in the SP513 study.
- 10.10. The Committee considered the evidence provided in the application supported that rotigotine is an effective dopamine agonist that has a similar effect to ropinirole and pramipexole, there was no evidence that it was superior to ropinirole and pramipexole, and some of the evidence was consistent with slightly less effectiveness. The Committee noted that the side-effect profile of rotigotine patches is similar to ropinirole and pramipexole. The Committee considered that there is currently a lack of evidence to support the use of rotigotine patches as monotherapy for advanced disease. Members considered that it was likely that the patches would in most cases be used in combination with oral levodopa therapy and possibly with oral ropinirole or pramipexole.
- 10.11. Members considered that a transdermal patch would provide little additional benefit compared with oral treatment for patients with advanced Parkinson's disease with swallowing difficulties, as this group of patients are likely to also require oral treatment, such as levodopa, and therefore will still need to take tablets. In addition, ropinirole and pramipexole can be crushed prior to administration if the patient has swallowing difficulties. The Committee also considered that patients with Parkinson's disease who have swallowing difficulties, and therefore likely to have other significant motor deficits, may also have problems with placement of the daily patch.
- 10.12. The Committee noted that the patch needs to be changed daily and that there is variability in the effectiveness of the patch depending on its placement on the body. The Committee considered that the patches are relatively large and considered that in some cases patients may require two patches.
- 10.13. Members considered that the patches would provide little added value for patients in the peri-operative period as in clinical practice pre-operative patients swallow their tablets with a small sip of water, and tablets can be crushed if required for any patients unable to swallow tablets post operatively, and in addition, steady state concentrations would not be reached for up to two days. However it may provide some value for patients undergoing upper gastrointestinal surgery or on total parenteral nutrition.

¹ Motor symptoms, in patients with Parkinson's disease, that are well controlled are referred to as the patient's "on" state; conversely periods of poor motor symptom control are referred to as "off" states.

- 10.14. The Committee considered that potential advantages of the patches include that its effectiveness is not affected by food and bypasses levodopa related gastroparesis. Members considered that in addition the supplier detailed in the submission that rotigotine does not promote pulsatile dopaminergic stimulation of neurones; and provides a continuous delivery of dopamine agonist. However members considered that the evidence basis for benefit from lack of pulsatile stimulation was theoretical only and not demonstrated in the outcomes reported in the clinical trials.
- 10.15. Members noted that there was a significant price differential between the 6 and 8 mg patch and were unclear of the rationale for this differential.
- 10.16. The Committee noted that pramipexole and ropinirole were both non-ergot dopamine agonists funded without restriction and did not consider there were currently any significant access problems. The Committee considered that funding rotigotine patches would be associated with considerable expenditure without significant additional health gain.
- 10.17. The Committee considered that the minutes from this discussion should be provided to the Neurological Subcommittee for their review at the next Subcommittee meeting.

11. Subcutaneous trastuzumab for HER 2 positive breast cancer

Application

- 11.1. The Committee considered a funding application from Roche Products NZ Ltd for the funding of subcutaneous trastuzumab (Herceptin SC) for the treatment of HER2 positive early, locally advanced or metastatic breast cancer. The Committee also considered a supporting application from The Breast Cancer Special Interest Group.

Recommendation

- 11.2. The Committee **recommended** that the application for subcutaneous trastuzumab for the treatment of HER2 positive early, locally advanced or metastatic breast cancer be declined. The Committee noted that there remained questions regarding the evidence and whether or not subcutaneous trastuzumab was cost neutral (or better) to the Health Sector taking into account practicable changes in service delivery, current intravenous trastuzumab costs and potential future entry of biosimilars.
- 11.3. 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; (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; (vii) The direct cost to health service users; and (viii) The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.*

Discussion

- 11.4. The Committee noted that currently intravenous (IV) trastuzumab (Herceptin) was funded for the treatment of HER2 positive early, locally advanced or metastatic breast cancer. Members noted that treatment was administered at a dose of 8 mg/kg for the first dose over 90 minutes, with subsequent maintenance doses of 6 mg/kg over 30 minutes every 3 weeks. Members noted that funding for early breast cancer was limited to 12 months duration (max cumulative dose 106 mg/kg) whereas treatment for metastatic disease was funded until disease progression. Members noted that the oral treatment lapatinib (Tykerb) was a funded alternative for HER 2 metastatic breast cancer, although uptake of this treatment was limited.

- 11.5. The Committee noted that this application was for an alternative subcutaneous formulation of trastuzumab that was administered at a fixed dose of 600mg/5mL over approximately 5 minutes, a substantially shorter period of time than is required for IV trastuzumab loading and maintenance doses. Members noted that SC trastuzumab is indicated for the same early breast cancer (eBC) and metastatic breast cancer (mBC) indications as IV trastuzumab, however, the SC trastuzumab does not have the IV formulation's indication for advanced gastric cancer. Members noted that the datasheet indicates that administration related reactions (ARRs) are known to occur with SC trastuzumab, and that SC trastuzumab should be administered by a healthcare professional prepared to manage anaphylaxis, and adequate life support facilities should be available and that treatment may be administered in an outpatient setting.
- 11.6. The Subcommittee considered the primary evidence for subcutaneous trastuzumab comprised an open label randomised Phase III trial in women with HER2-positive stage I to IIIC breast cancer (the enHANced treatment with NeoAdjuvant Herceptin [HannaH] study, Ismael G et al Lancet Oncol 2012; 13(9): 869-78). Members noted that this study enrolled 596 women with HER2-positive, operable, locally advanced or inflammatory breast cancer, patients were randomised 1:1 to receive 8 cycles of neoadjuvant chemotherapy administered concurrently with trastuzumab every 3 weeks either intravenously (8 mg/kg loading dose over 90 minutes, 6 mg/kg maintenance dose over 30 minutes (n=299)) or subcutaneously (fixed dose of 600 mg in 5 mL over 5 minutes (n=297)). Members noted that chemotherapy comprised 4 cycles of docetaxel (75 mg/m²) followed by four cycles of fluorouracil (500 mg/m²), epirubicin (75 mg/m²), and cyclophosphamide (500 mg/m²), every 3 weeks. After surgery, patients continued trastuzumab to complete 1 year (18 cycles) of treatment. Members noted that SC trastuzumab was injected into the thigh with a hand-held syringe at a steady rate over about 5 min by the nursing team at alternating sites.
- 11.7. The Committee considered that this study was moderate in strength, quality and relevance to the New Zealand population noting that in New Zealand most patients currently did not receive neoadjuvant (pre-surgery) trastuzumab.
- 11.8. The Committee noted that the co-primary endpoints of the study were C_{trough} recorded before surgery (predose cycle 8) and pathological complete response (pCR) with these analysed on a per-protocol basis because patients needed to achieve an 8th cycle of chemotherapy and have surgery in order to have these endpoints assessed.
- 11.9. The Committee noted that results indicated that SC trastuzumab was non-inferior to IV trastuzumab in terms of C_{trough} before surgery: the geometric mean ratio was 1.33 (90% CI 1.24–1.44), with the lower limit of the two-sided 90% CI being greater than the prespecified non-inferiority margin. The Committee further noted that SC trastuzumab was non-inferior to IV trastuzumab in terms of the proportion of patients who achieved a pCR: 118 (45.4%) of 260 patients in the SC group and 107 (40.7%) of 263 in the IV group achieved a pCR.
- 11.10. The Committee noted that in the Trail Profile CONSORT diagram for the study (Figure 2 Ismael G et al Lancet Oncol 2012; 13(9): 869-78) the number of patents who had surgery were n=278 for the IV group compared with n=275 for the SC group, whereas the number of patients included in the per-protocol C_{trough} analysis were n=235 for IV and n=234 for SC, a shortfall of around 15% and the number of patients included in the pCR analysis were n=263 for IV and n=260 for SC, a shortfall of around 5%. Members could not identify reasons for these shortfalls from the publication.
- 11.11. The Committee noted that both treatment groups reported a similar incidence of grade 3-5 adverse events, however, members noted that there were more serious adverse events in the SC group, principally infections (4.4% IV vs. 8.1% SC). Members noted that the authors considered that this may have been due to reporting bias in this open label study. Members noted that four adverse events led to death (one in the IV group and three in the

SC group), all of which occurred during the neoadjuvant phase and of these, two, both in the SC group, were deemed to be treatment related.

- 11.12. The Committee noted evidence from an open label, 2-part, phase I/II dose finding study conducted in New Zealand and Australia (Wynne C et al *J Clin Pharmacol* 2013; 53(2): 192-201) the results of which were used as a basis for the 600mg/5mL fixed dose used in the HannaH study. Members noted that this was a dose finding study that made intra-patient comparisons of weight based SC and IV dosing (6-12 mg/kg SC vs 6 mg/kg IV) in healthy male volunteers (HMs) and women with HER2-positive early breast cancer (patients). Members considered that comparisons between the HMs and patients populations was not ideal, noting in particular that the HMs had lower mean body mass index (BMI) compared with the patients which may impact pharmacokinetics and pharmacodynamics of trastuzumab. Members considered that the range of mean BMI across both populations was relatively narrow and considered that there was a risk that the fixed dose may lead to under, or over, dosing in severely overweight or underweight patients respectively.
- 11.13. The Committee noted evidence from an international open label randomised cross over patient preference study in women with HER2-positive early breast cancer (the PrefHer study, Pivot et al *Lancet Oncol* 2013; 14: 962-70). Members noted that this study used telephone interviews to determine patient preference for route of administration of trastuzumab. Members noted that 248 patients were randomised 1:1 to receive four cycles of SC trastuzumab a fixed dose of 600 mg/5 mL followed by four cycles of standard 6 or 8 mg/kg IV trastuzumab or the reverse sequence. Members noted that SC trastuzumab was injected into the thigh using the single-use injection device (Cohort 1) or hand-held syringe (Cohort 2) over 5 min. Members noted that SC trastuzumab via the single-use injection device (Cohort 1) was preferred by 216 patients (91.5%, 95% CI 87.2-94.7; $p < 0.0001$), 16 patients preferred IV trastuzumab (6.8%, 3.9-10.8), and four had no preference (1.7%, 0.5-4.3). Unpublished results from Cohort 2 were similar to Cohort 1: SC trastuzumab administered by hand held syringe was preferred by 199 patients (86%, 95% CI 81-90%; $p < 0.0001$); 29 preferred IV (13%, 95% CI 9-18%), and 3 had no preference (1%, 95% CI 0-4%). The two main reasons for preference stated by patients were either it saved time or caused less pain and discomfort.
- 11.14. The Committee noted that observational time and motion (TAM) sub-studies were undertaken within the PrefHer study to quantify health care professional (HCP) time associated with preparation and delivery of IV and SC trastuzumab and the duration that patients sat in infusion chairs. Members noted that an analysis in UK centres published by Burcombe et al (*Adv Breast Can Res.* 2013;2:133-40) showed a mean time saving of 68 minutes for SC administration over IV administration per treatment cycle.
- 11.15. The Committee noted a draft unpublished manuscript from a TAM study in two New Zealand centres participating in SafeHer, an ongoing multicenter, two-cohort, non-randomized, open-label study that is evaluating the safety and tolerability of SC and IV trastuzumab as adjuvant therapy in patients with early HER2-positive breast cancer. Members noted that the authors, one of which was a Roche employee, concluded that the use of SC trastuzumab reduced mean chair time by 36.95 minutes, total nurse time by 6.12 minutes and pharmacist time by 17 minutes per patient per cycle (total estimated HCP cost saving of NZ \$61.67). After adding consumable cost savings (estimated to be NZ \$15.27 per patient per cycle), the overall saving with SC trastuzumab vs IV was NZ \$76.84 per patient per cycle. Members noted that the authors considered that in reality the cost savings would be greater because this study excluded costs of indwelling IV catheter insertion and maintenance, management of complications and did not factor in costs incurred by the patient either directly (e.g. transport, parking) or indirectly (e.g. time and loss of productivity for both patients and their caregivers).
- 11.16. The Committee noted that all of the studies provided compared SC with IV treatment when administered as a single agent and no data was provided comparing SC with IV trastuzumab when given in combination with other IV chemotherapy. Members

considered that the time savings demonstrated in the TAM studies were only relevant for the subset of patients receiving single agent trastuzumab, for example well established HER 2 positive metastatic breast cancer patients. Members considered that for patients receiving concurrent chemotherapy or those whom are newly diagnosed and requiring closer management or support the overall time savings would likely be less. Members considered that patients who were receiving concurrent chemotherapy would most likely already have a Central Venous Access Device (CVAD) or tunnelled CV line in place for their other chemotherapy treatments, therefore administration of IV trastuzumab in these patients would be unlikely to be associated with increased pain and discomfort. Members acknowledged that following completion of chemotherapy the CVAD or CV line could be removed earlier and SC trastuzumab would be more convenient than IV for subsequent single agent doses of trastuzumab.

- 11.17. The Committee considered that overall SC would be more convenient and preferred by patients receiving single agent trastuzumab. Members considered that the benefits for patients receiving concurrent chemotherapy were unclear. The Committee noted that all the studies comparing IV and SC formulations of trastuzumab were conducted in patients with HER 2 positive early breast cancer and no data was provided in women with HER 2 positive metastatic breast cancer which members considered would be the patient group that would most benefit from SC trastuzumab.
- 11.18. The Committee disagreed with the supplier's view that at the pricing proposed SC trastuzumab would be cost neutral, in terms of drug cost, with IV trastuzumab. Members considered that the supplier had overestimated the average cost per dose of IV trastuzumab treatment and the average number of cycles administered.
- 11.19. The Committee noted that IV trastuzumab currently consumes a large proportion of cancer centres' infusion capacity, however, members disagreed with the supplier's view that SC trastuzumab would be cost saving to DHBs when taking into account reduced chair and HCP time. Members considered that it was not appropriate to apply HCP and time savings to all patients for all cycles of treatment for the reasons outlined above. In addition, members considered that resource savings from reduced chair and HCP time would most likely be redirected to other patients receiving other treatments meaning that SC trastuzumab would have the effect of increasing DHB capacity rather than creating cost savings for DHBs. Members noted that such increased capacity and costs would likely be associated with some health gain. Members noted that SC trastuzumab had the potential to be administered in the community, for example at a GP practice, but that at present these services are not in place and the associated costs were unknown.
- 11.20. The Committee noted that the EU patent for IV trastuzumab had recently expired and biosimilar versions of IV trastuzumab were in late stage development. Members considered that biosimilar trastuzumab could be available in NZ in the next 2-3 years and would likely lead to substantial cost savings. Members noted that the patent for SC trastuzumab did not expire until 2030 and that none of the suppliers' cost analyses for SC trastuzumab factored in lower costs for IV trastuzumab in the future following biosimilar entry. Members noted that the supplier was not seeking delisting or subsidy protection for SC trastuzumab which it considered would allow PHARMAC the opportunity to run a competitive process for trastuzumab sole supply in the future. However, members considered that if SC trastuzumab was funded and gained significant market share over the IV formulation it would significantly limit the savings that could be achieved from biosimilar competition.
- 11.21. The Committee considered that SC trastuzumab would be more convenient and less painful than IV trastuzumab for some patients and it would likely free up some DHB hospital resources, however, members noted there remained many unanswered questions regarding the extent of resource changes and the costs or costs savings that would be realised in practice. Members also considered that any analysis for SC trastuzumab needed to consider the counterfactual of delaying or reduced impact of savings from biosimilar IV trastuzumab entry.

12. Umeclidinium with vilanterol for the treatment of COPD

Application

- 12.1. The Committee reviewed an application from GlaxoSmithKline for the listing of the combination umeclidinium with vilanterol (Anoro Ellipta) inhaler on the Pharmaceutical Schedule.

Recommendation

- 12.2. The Committee **recommended** the application be declined.
- 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 the application was for funding a combination inhaler containing 62.5 mcg of a long-acting muscarinic receptor (LAMA), umeclidinium, and 25 mcg of a long-acting beta₂-adrenoceptor agonist (LABA), vilanterol, for the treatment of chronic obstructive pulmonary disease (COPD). The Committee noted that neither active ingredient was available on its own as a single agent inhaler. The Committee noted Anoro Ellipta is a dry powder inhaler indicated for once daily use for the treatment of COPD. [REDACTED]
- 12.5. The Committee noted the clinical studies included in the supplier's submission were in the form of clinical study reports or clinical study summaries. Three published papers were included with the application:
- 12.6. Donohue et al. *Respir Med.* 2013;107(10):1538-46. This was a double blind placebo randomised, parallel group study evaluating the efficacy and safety of 24 week treatment with once daily umeclidinium/vilanterol (UMEC/VI) (62.5/25 mcg) compared with monotherapies (umeclidinium 62.5 mcg and vilanterol 25 mcg separately) and placebo, involving 1,532 patients with moderate to severe COPD. All treatment groups resulted in significant improvements in trough FEV₁ on Day 169 versus placebo (72-167 mL; all P<0.001), but the increase with UMEC/VI was greater than that observed with monotherapies (52-95 mL; all P≤0.004). Compared with placebo, the combination UMEC/VI product was associated with reduced use of rescue therapy, improved the transition dyspnea index (TDI), mean shortness of breath with daily activity (SOBDA) score and the St George's Respiratory Questionnaire (SGRQ) score as a measure of health-related quality of life. No significant changes in vital signs, electrocardiography or laboratory parameters were observed.
- 12.7. Celli et al. *Chest* 2014; 145: 981-91. This was a double-blind, placebo controlled, parallel-group study with 1493 patients assigned to 24 weeks treatment with UMEC/VI 125/25 mcg, UMEC 125 mcg, VI 25 mcg or placebo. All the active treatments resulted in significantly improved trough FEV₁ versus placebo (124-238 mL; all P<0.001); with significantly greater functional benefit of combination therapy over monotherapy (79-114; all P<0.001). The combination therapy showed improvements in the TDI, rescue medication use and health related quality of life. The study did not report any safety concerns, and the numbers of adverse events were similar across all study arms.
- 12.8. Decramer et al. *Lancet Respir Med.* 2014; 2: 472-86. In two multicentre, randomised, blinded, double-dummy, parallel-group active controlled trials, patients were assigned to treatment with either UMEC 125 mcg / VI 25 mcg, UMEC 62.5 mcg / VI 25 mcg, TIO 18

mcg and either VI 25 mcg (Study 1, n=1141) or UMEC 125 mcg (Study 2, n=1191). In Study 1 (843 COPD patients after exclusions), significant improvements in least squares mean change from baseline trough FEV₁ and 0-6 hours weighted mean FEV₁ were observed with both combination therapies compared with the monotherapies (P<0.005). In Study 2 (869 COPD patients after exclusions), treatment with the combination therapies resulted in statistically significant improvement in trough FEV₁ at day 169 compared with tiotropium 18 mcg (P=0.003) but not compared with umeclidinium 125 mcg (P=0.142). All treatments produced improvements in dyspnoea and health-related quality of life.

- 12.9. Members considered the evidence presented to be of reasonably good quality and strength in terms of the combination umeclidinium/vilanterol product being effective compared with placebo and being slightly more effective than tiotropium alone. However, members noted that the application did not include any clinical studies comparing umeclidinium/vilanterol against single LABA plus LAMA products (eg a tiotropium inhaler plus a salmeterol inhaler) and so it is unclear as to whether the combination umeclidinium/vilanterol product is as effective as taking a LABA and a LAMA as separate inhalers. As the place in treatment of the combination product is after monotherapy has failed, members considered the appropriate comparator would be either two single agents (LAMA inhaler plus LABA inhaler) or a combination product (the ICS/LABAs - fluticasone with salmeterol inhaler or budesonide with eformoterol inhaler or, preferably, other LAMA/LABA combinations such as glycopyrronium bromide/indacaterol maleate, aclidinium bromide/formoterol, and tiotropium bromide/olodaterol) and no published clinical studies have been presented comparing the umeclidinium with vilanterol combination with either glycopyrronium or indacaterol.
- 12.10. The Committee noted that the individual components, umeclidinium and vilanterol, are not available as monotherapy products in New Zealand, which means stepwise incremental dose titration approaches to treatment are not possible with these components. Members considered there may be some safety issues as patients may use the UMEC/VI combination product alongside another LAMA or LABA, and that while the data sheet states the product is not recommended for asthma patients there is a risk that it may be prescribed for this patient group. The Committee noted that while it may be beneficial to have a once a day product, many patients tend to inhale their products several times until they feel they experience symptom relief, which may increase the number of inhalers dispensed and the frequency of adverse reactions experienced. Members noted that while there appeared to be more adverse events reported for the combination umeclidinium/vilanterol product over single agents there were no significant new safety issues.
- 12.11. The Committee noted that FEV₁ is a physiological marker of lung function that has a poor relationship with patient-centred outcomes such as quality of life and exacerbations, so that changes in FEV₁ cannot be used to reliably predict improvements in quality of life or reductions in the number of exacerbations. The Committee noted that the data on Anoro Ellipta is too new to the market to have generated sufficient long term data to reliably indicate survival benefit, and no hospitalisation data was offered in the clinical studies. The Committee recommended PHARMAC ask the supplier to provide further data on the effect that treatment with umeclidinium with vilanterol has on exacerbations and hospitalisation rates.
- 12.12. The Committee considered the product would be used for a long period of time in a large patient population posing a fiscal risk. Overall the Committee considered the data to be too immature and that further clinical study results were required on the effect Anoro Ellipta has on exacerbation and hospitalisation rates and comparative studies with the currently funded LAMAs and LABAs used together. The Committee recommended the application be declined but that PHARMAC request further information from the supplier on the long term benefits of Anoro Ellipta.

13. Fluticasone with vilanterol for asthma and COPD

Application

- 13.1. The Committee reviewed an application from GlaxoSmithKline for the listing of the combination fluticasone furoate with vilanterol (Breo Ellipta) inhaler on the Pharmaceutical Schedule for the treatment of patients with asthma and COPD.

Recommendation

- 13.2. The Committee **recommended** the application to list the high strength fluticasone furoate 200 mcg in combination with vilanterol 25 mcg be declined.
- 13.3. The Committee **recommended** listing fluticasone furoate 100 mcg in combination with vilanterol 25 mcg on the Pharmaceutical Schedule with a low priority.
- 13.4. 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 Māori and Pacific peoples (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things.*

Discussion

- 13.5. The Committee noted the application was for (1) open listing of the once daily dry powder inhaler containing fluticasone furoate 100 mcg in combination with 25 mcg of vilanterol for the treatment of asthma and COPD, and (2) listing the high dose once daily dry powder inhaler containing fluticasone furoate 100 mcg in combination with 25 mcg of vilanterol for the treatment of asthma under Special Authority endorsed by a specialist.
- 13.6. The Committee noted that Breo Ellipta contains two new compounds – fluticasone furoate (FF) and vilanterol (VI). Fluticasone furoate is a novel inhaled corticosteroid in that it is structurally different from fluticasone propionate, having an ester derived from 2-furoic acid at the C-17 α position that replace the simpler propionate ester, conferring both greater affinity for the GC receptor and longer retention in respiratory tissues than fluticasone propionate. Fluticasone furoate has 24 hour action and appears to be four times as potent as fluticasone propionate. The committee considered that among the currently available inhaled corticosteroid formulations, beclomethasone dipropionate 480 mcg, budesonide 1,200 mcg fluticasone propionate 400-500 mcg could be therapeutically equivalent to 100 mcg of fluticasone furoate even though direct comparisons were not available (William H Kelly. The Annals of Pharmacotherapy. 2009;43:519-27). The Committee noted that vilanterol has been shown to have a significantly faster onset of action than salmeterol (3.1 minutes versus 8.3 minutes) and a significantly longer duration of action.
- 13.7. The Committee noted that in New Zealand, patients have open access to Seretide containing a twice-a-day slow acting LABA, restricted access to Symbicort and Vannair containing a twice daily fast acting LABA with low potency ICS, and open access to the rapid-acting once-daily LABA indacaterol, and restricted access to two LAMAs.
- 13.8. The Committee noted that there were a large number of clinical studies included in the submission but that the applicant had not submitted a number of peer review publications despite being available. The Committee noted the trials appeared to be well conducted but the submission was of average to poor quality.

Chronic Obstructive Pulmonary Disease (COPD)

- 13.9. The Committee noted that there were four head-to-head studies between fluticasone furoate with vilanterol and fluticasone propionate with salmeterol, three of these studies being between fluticasone furoate with vilanterol (100/25) and fluticasone propionate with salmeterol (250/50) and published in one paper (Dransfield et al. Respiratory Medicine 2014; 108:;1071-9). The studies were similar in design and concept and enrolled patients

who were ≥ 40 years of age with a clinical history of COPD, post salbutamol FEV₁/FVC ratio of ≤ 0.70 and FEV₁ $\leq 70\%$ and a ≥ 10 pack per year history of cigarette smoking.

- 13.10. Following a run-in period, patients were randomised (1:1) to fluticasone furoate with vilanterol 100/25 mcg once daily in the morning via dry powder inhaler or fluticasone propionate with salmeterol 250/50 mcg twice daily via the Accuhaler for 12 weeks. The primary efficacy endpoint was the differences between treatment groups in change from baseline trough in 0-24 hour weighted mean FEV₁. Of the 2,465 patients screened across the three studies, 1858 were randomised. The Committee noted that there was no significant improvement in FEV₁ in Study 2 and 3 but there was an improvement in Study 1. Pooled analysis showed significant improvement in the weighted mean 0-24 hour FEV₁ between the groups (least square mean of 41, 9 0.0001). In pooled analysis the onset of action was 4 minutes faster for the fluticasone furoate with vilanterol product and there was improvement in the baseline trough FEV₁ by 39mL mainly because of Study 1.
- 13.11. The Committee noted the fourth study was of similar design but compared once daily fluticasone furoate with vilanterol (100/25) against twice daily higher dose fluticasone propionate with salmeterol (500/50). The difference in improvement from baseline in 0-24 hour weighted mean FEV₁ on day 84 did not reach statistical improvement between the two treatments and the proportion of rescue-free 24 hour periods was similar between the two periods. The Committee noted that 9 patients in the fluticasone furoate with vilanterol arm had cardiac disorders (6 of which lead to withdrawal) compared to one in the fluticasone propionate with salmeterol arm.
- 13.12. The Committee noted that the pooled analysis of two clinical studies were published by Dransfield et al (Lancet Resp Disease 2013;1:210-13). The two studies were identical in design and compared three strengths of fluticasone furoate with vilanterol (50/25 mcg; 100/25 mcg and 200/25 mcg) to vilanterol 25 mcg. The Committee noted that in the pooled analysis significantly fewer moderate and severe exacerbations were noted in the FF/VI groups than in the vilanterol only group. However in one study there was no difference in exacerbations between FF/VI and VI groups. Eight deaths from pneumonia were noted in the FF/VI groups compared with none in the vilanterol only group. Seven of these deaths occurred in high dose FF/VI group and four deaths occurred in one site. The Committee noted the differences between fluticasone furoate 100 mcg and 200 mcg seem to be marginal in terms of efficacy.
- 13.13. The Committee reviewed a number of other studies (HZC112207 (Fernando J Martinez Resp Med Apr 2013;107:550-9); HZC112206 (Kerwin et al Resp Med Apr; 107:560-9); and HZC110946 (Bossica et al Clin Ther. 2012;34:1655-66)). The Committee noted that studies HZC113684, HZC114156, HZC115805 and HZC115247 were not included in the submission in any form, although one was confined to a 52 week safety study involving Japanese patients. There was no reason why such study reports or publications were not included in the submission.
- 13.14. The Committee noted that Oba et al published a meta-analysis of LABA and combination ICS/LABAs to assess their efficacy in the prevention of COPD exacerbations (J Chron Obstruct Pulmon Dis. 2014;9:469-479). The authors concluded that the combinations have a class effect with regard to the prevention of COPD exacerbations and indicated that moderate dose ICS/LABA therapy would be sufficient for COPD patients when indicated. The efficacy of ICS/LABA therapy appeared modest and had no impact in reducing severe exacerbations.
- 13.15. In summary the Committee considered the quality of evidence for comparative effectiveness in COPD to be good; there to be no difference in effectiveness between fluticasone furoate with vilanterol and fluticasone propionate with salmeterol; higher dose FF may be associated with increased risk of pneumonia and in two studies the combination of FF/VI product did not indicate clinically or statistically significant improvements in effectiveness compared with VI alone.

Asthma

- 13.16. The Committee reviewed the pivotal trial on asthma by Woodcock et al. (Chest 2013;144:1222-9). The aim of the study was to compare the efficacy of fluticasone furoate with vilanterol and fluticasone propionate against salmeterol in patients with persistent asthma uncontrolled on a medium dose inhaled corticosteroid. This was a double blind, double dummy, parallel study with 806 patients randomised to receive either FF/VI (100/25 mcg) once daily or FP/SAL (250/50 mcg) twice daily. The primary efficacy measure was improvements from baseline in FEV₁ after 24 hours of treatment. Improvements were observed with both treatments but the adjusted mean treatment difference was not statistically significant. There were no differences between the two treatments between the 0 to 4 hour serial weighted mean FEV₁, trough FEV₁, asthma control, quality of life questionnaire and time to onset of bronchodilator effects. There was also no difference in the reported exacerbations between the two treatments. Both treatments were well tolerated, with no clinically relevant effect on urinary cortisol excretion or vital signs and no treatment –related serious adverse events.
- 13.17. The Committee reviewed a phase III clinical trial conducted by Bateman et al (Thorax 2014;69:312-9) which was a randomised, multicentre, double blind, parallel-group study enrolling 1792 patients in a 52 week trial comparing fluticasone furoate with vilanterol (100/25 mcg, n=889) and fluticasone furoate (100 mcg, n=903). The adjusted probability of experiencing a severe asthma exacerbation by 52 weeks was 15.9% (95% CI 13.5% to 18.2%) in the FF 100 mcg group and 12.8% (95% CI 10.7% to 14.9%) in the FF/VI 100/25 mcg group. Compared with FF, FF/VI delayed the time to first exacerbation (HR 0.795, 95% CI 0.642 to 0.985). Significantly greater improvements in the ACQ7 score were observed in patients receiving FF/VI compared with FF at all timepoints (p<0.001; week 12, week 36 and endpoint). Similar proportions of patients experienced severe asthma exacerbations leading to hospitalisation with FF (n=9, <1%) and FF/VI (n=8, <1%). In the FF group, 26 (3%) patients visited an emergency department or urgent care clinic due to a severe asthma exacerbation and 142 (14%) made unscheduled visits to a healthcare provider. These frequencies were 22 (2%) and 119 (12%), respectively, for FF/VI.
- 13.18. The Committee also reviewed three lung function studies – clinical study reports HZ106829; HZ1068270 (Bleeker et al. J All Clin Immunol Pract 2014;2:553-61) and HZ106839 (Buse et al Thorax doi:10.1136/thoraxjnl-2012-202606).
- 13.19. The Committee considered the quality of comparative effectiveness between fluticasone furoate with vilanterol and fluticasone propionate with salmeterol to be high and considered there to be no difference in effectiveness between the two products, which aligned with the supplier's comparative analysis of treatments. The Committee noted that there are no other once daily ICS/LABA combination products currently available on the market.
- 13.20. The Committee considered that although these products are indicated for once-daily use there may be a number of patients who will have more than one puff per day, especially if it is used as a reliever due to fast onset action of VI and that this may cause a safety risk as the more potent steroids and LABAs at higher doses could cause adverse effects. The committee was also concerned with the number of inhaled products available in the market and the potential for confusion associated with their usage. However, the committee also considered that once daily combination may be convenient for some patients and potentially could improve adherence.
- 13.21. As per the Committee's earlier advice on listing a high dose fluticasone (November 2000, February 2001, November 2007, November 2010 and August 2011), the Committee was not supportive of listing the high dose inhaled corticosteroid and recommend that submission to list the fluticasone furoate 200 mcg in combination with vilanterol 25 mcg presentation be declined.

- 13.22. The Committee recommended that, as the clinical studies have indicated fluticasone furoate with vilanterol to be the same or similar to fluticasone propionate with salmeterol, the product Breo Ellipta be listed on the Pharmaceutical Schedule at the same net price as Seretide or generics that may be listed in the future.

14. Micafungin powder for injection (Mycamine)

Application

- 14.1. The Committee considered a funding application from bioCSL for the listing of Mycamine (mycalfungin powder for injection) for the treatment of invasive candidiasis, for the treatment of oesophageal candidiasis in patients aged 16 and over for whom intravenous therapy is inappropriate, and for prophylaxis of *Candida* infection in children and adult patients undergoing allogenic haematopoietic stem cell transplantation or patients who are expected to have neutropenia.

Recommendation

- 14.2. The Committee deferred making a recommendation on the funding of Mycamine (mycalfungin powder for injection) pending review of the application by the Anti-Infective Subcommittee of PTAC.

Discussion

- 14.3. The Committee noted that that micafungin is an echinocandin, a class of antifungal drugs that are semisynthetic lipoproteins produced via chemical modifications of natural products of fungi. Members noted that echinocandins work as non-competitive inhibitors of 1,3-beta-D-glucan synthase, and to a lesser extent 1,6-beta-D-glucan synthase. The Committee noted that the proportion of fungal cell wall composed of glucan varies widely between different species of fungi; 1,3-beta-D-glucan is more predominant in the cell wall of *Candida* and *Aspergillus* species than in yeast forms of dimorphic fungi. The Committee noted that echinocandins do not have activity against *Cryptococcus*, *Zygomycetes*, *Fusarium* or *Scedosporium* fungi. The Committee noted that caspofungin is also an echinocandin.
- 14.4. The Committee noted that the echinocandins have low oral bioavailability, high protein binding and low cerebrospinal fluid and urine concentrations. The Committee noted that echinocandins are not dialyzable, do not need dose adjustment in patients with renal impairment, and considered them to be generally well tolerated.
- 14.5. The Committee noted that echinocandins are registered for various indications based on clinical trial data for each medication rather than in vitro data. The Committee noted that caspofungin is registered for invasive *Aspergillus* refractory to other treatments where there is intolerance to other agents; the Committee further noted that Mycamine is not indicated for use in *Aspergillus* infection in New Zealand.
- 14.6. The Committee noted that although micafungin is not registered for use in *Aspergillus*, it is considered to have similar clinical efficacy to caspofungin for this indication. The Committee noted a single, open label, non-comparative study (Chen et al. *Drugs*. 2011;71:11-41) which demonstrated a favourable response in 6 of 12 patients who received micafungin monotherapy as primary treatment and 9 of 22 patients who received micafungin as salvage therapy for *Aspergillus* infection. Furthermore the Committee also noted that these results indicated that the minimum effective concentration for micafungin was 2 fold to 10 fold lower when compared to caspofungin. The Committee considered that the strength and quality of evidence for the use of micafungin in *Aspergillus* was weaker than that for its use in *Candida* infection.
- 14.7. The Committee noted that in general, in vitro and in vivo activity against *Candida* species is considered to be comparable amongst the three echinocandins caspofungin,

micafungin and anidulafungin. The Committee noted a study of 595 patients using either micafungin (100 mg or 150 mg daily) versus caspafungin (70 mg followed by 50 mg daily) for the treatment of invasive candidiasis (Pappas et al. Clin Inf Dis. 2007;45:883) in which micafungin demonstrated non-inferiority to caspafungin.

- 14.8. The Committee noted that, in New Zealand, azole resistance to the three most predominant species of *Candida* (*C. albicans*, *C. glabrata* and *C. parapsilosis*) is considered to be low. The Committee noted that uncertainty exists as to whether in vivo resistance occurs with *Aspergillus*, however it also considered that treatment outcomes in patients with invasive fungal infections treated with echinocandins remain less than optimal.
- 14.9. The Committee noted that the supplier application identified no additional benefit of micafungin over caspofungin other than cost. The Committee noted that micafungin is the only echinocandin that does not require a loading dose. The Committee questioned the information presented by the applicant on cost and noted that this would be dependent on factors such as the dosage used, i.e. 150 mg versus 100 mg daily, and whether micafungin was used only for its registered indications.
- 14.10. The Committee deferred making a recommendation on the application pending advice from the Anti-Infective Subcommittee of PTAC on the following issues:
- Whether there are any advantages of micafungin over the currently available funded treatments;
 - How micafungin would be used in practice;
 - The anticipated dose of micafungin.

15. Epoprostenol for pulmonary arterial hypertension

Application

- 15.1. The Committee considered a funding application from Actelion for the listing of epoprostenol (Veletri) in the Pharmaceutical Schedule for the treatment for patients with late stage pulmonary arterial hypertension (PAH).

Recommendation

- 15.2. The Committee **recommended** that epoprostenol (Veletri) be listed in Section H of the Pharmaceutical Schedule as a bridge to transplant for patients with PAH who are on the active waiting list for lung transplantation with a high priority.
- 15.3. 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

- 15.4. The Committee noted that epoprostenol is a prostacyclin analogue delivered via a continuous infusion via an indwelling central venous line. The Committee also noted that the alternative IV prostacyclin analogue that is currently listed in Section H of the Pharmaceutical Schedule is iloprost injection.
- 15.5. The Committee noted a retrospective longitudinal follow-up study by Hoepfer et al (Eur Respir J 2009;34:132-7) which observed the clinical course of 79 patients with PAH

following treatment with IV iloprost. In most cases these patients had received inhaled iloprost as first-line therapy. The Committee considered this evidence to be weak and of poor quality. The Committee considered that poor survival outcomes at 1, 3 and 5 years occur in patients being treated with IV iloprost. The Committee considered that, compared with outcomes published for IV iloprost for patients in different settings (Higenbottam et al. Heart. 1998;80:151-5), IV epoprostenol may offer additional survival benefits.

- 15.6. The Committee noted an open labelled, randomised controlled trial on the use of continuous IV epoprostenol in 111 patients with moderate to severe pulmonary hypertension measured over a 12 week period (Badesch et al. Ann Intern Med 2000; 132:425-434). Members noted that the trial indicated that added epoprostenol significantly improved exercise capacity, function/symptoms and cardiopulmonary dynamic surrogate markers compared with conventional treatments alone; however it did not indicate that epoprostenol provided a statistically significant mortality benefit.
- 15.7. The Committee noted a systematic review on the effect of PAH -specific therapies on health related quality of life (Rival et al. Chest. 2014;146:686-708). Members considered that, although epoprostenol used in combination with sildenafil demonstrated improvements in health related quality of life, the increase in quality of life scores associated with PAH treatments may not be significant clinically.
- 15.8. The Committee noted a meta-analysis on the survival outcomes of prostanoid therapy for PAH (Zheng et al. Eur J Clin Pharmacol. 2014; 70:13-21). Members noted that at week 13 there was a 44% decrease in mortality for those patients treated with prostanoids, and subgroup analysis indicated that only treatment with IV prostaoids was associated with a reduction in mortality. The Committee considered that there is a significant risk of potentially serious adverse reactions, including sepsis, with the use of this method of administration. The Committee noted that, with respect to the effects of epoprostenol, beraprost, iloprost and trepostinil, there was no statistical heterogeneity between groups in subgroup analysis for total mortality.
- 15.9. The Committee noted a letter from the New Zealand Lung Transplant Unit in relation to the use of epoprostenol as a bridge to lung transplant. The Committee noted that patients with PAH who are on the active lung transplant waiting list would already have progressing disease despite maximal inhaled or oral therapy and that the Unit considers that a switch in therapy to IV epoprostenol would improve survival outcomes (for successful pulmonary transplantation) in this patient population whilst awaiting donor availability. The Committee considered the health need in this patient population to be high.
- 15.10. The Committee noted the recommendations by the PBAC in Australia in relation to epoprostenol and its conclusion that IV epoprostenol was non-inferior to bosentan and inhaled iloprost in terms of comparative efficacy. The Committee considered that the use of IV epoprostenol in combination with sildenafil has been validated, but however considered that bosentan in combination with epoprostenol has not been validated.
- 15.11. The Committee considered the supplier's estimate of daily dose of prostacyclin treatment to be an underestimate and an average daily dose of 3.26mg of epoprostenol or 130mg of iloprost to be more appropriate.