

PTAC meeting held 4 & 5 November 2010

(minutes for web publishing)

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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 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.

Some material has been withheld, in accordance with the Official Information Act 1982 (OIA) to:

- protect the privacy of natural persons (section 9(2)(a));
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Contents

1	Subcommittee minutes	3
2	Lacosamide (Vimpat) for treatment resistant epilepsy.	4
3	Azacitidine (Vidaza) for myelodysplastic syndromes.....	5
4	Varenicline (Champix) for smoking cessation	5
5	Benzbromarone for gout.....	5
6	Dornase alfa for cystic fibrosis	9
7	Rifabutin (Mycobutin) for refractory helicobacter pylori treatment	13
8	Imiglucerase (Cerezyme) for Type 1 and Type 3 Gaucher disease	14
9	Miglustat (Zavesca) for mild to moderate Type 1 Gaucher disease	16
10	Voriconazole (Vfend) for invasive aspergillus and resistant candidiasis	18
11	Posaconazole (Nofaxil) for prophylaxis of invasive aspergillus	20
12	Dabigatran (Pradaxa) for stroke, systemic embolism, atrial fibrillation	21
13	Bortezomib for AL amyloidosis	24
14	Lapatinib for metastatic breast cancer	25
15	Nab-paclitaxel (Abraxane) for advanced breast cancer	26
16	Fluticasone/salmeterol (Seretide) for asthma.....	28
17	Rivastigmine patches (Exelon) for Alzheimer's disease	32
18	Adalimumab (Humira) for juvenile idiopathic arthritis	33
19	Paracetamol with ibuprofen (Maxigesic) for analgesia	35
20	Modafinil (Modavigil) for narcolepsy	38

1 Subcommittee minutes

1.1 Respiratory Subcommittee Minutes – 5 July 2010

1.1.1 The Committee noted the Subcommittee's recommendation regarding montelukast for preschool wheeze. The Committee noted that it had not reviewed the data and therefore could not accept the Subcommittee's recommendation. The Committee **recommended** that it review the montelukast funding proposal.

1.1.2 The remainder of the record of the meeting was noted and accepted.

1.2 Cancer Treatments Subcommittee Minutes – 20 August 2010

1.2.1 The Committee noted the Subcommittee's recommendation to list gemcitabine as adjuvant treatment for patients with macroscopically resected pancreatic cancer with a high priority. The Committee noted that in November 2009 it had declined to list gemcitabine for this indication.

1.2.2 The Committee reiterated its view that the evidence demonstrated no survival benefit for gemcitabine compared with the Mayo 5FU chemotherapy regimen in patients with resected pancreatic cancer. However, the Committee noted the Subcommittee's concerns that New Zealand oncologists did not use the Mayo 5FU chemotherapy regimen in this population because it is considered too toxic and is relatively intensive to deliver, and therefore, most patients would currently receive either best supportive care or weekly 5FU chemotherapy, for which there was no evidence.

1.2.3 The Committee **recommended** that gemcitabine should be funded for the adjuvant treatment of macroscopically-resected pancreatic cancer with a low priority.

1.2.4 The remainder of the record of the meeting was noted and accepted.

1.3 Special Foods Subcommittee Minutes – 21 May 2010 and 14 June 2010

1.3.1 The Committee reviewed the minutes from the Special Foods Subcommittee meetings of 21 May 2010 and 14 June 2010.

1.3.2 The Committee noted that the Special Authority restrictions on adult standard powder, sip and enteral feeds were loose and ill-defined.

- 1.3.3 The Committee considered that the most significant influence on access currently is the specialist requirement. The resultant inequity of access was a problem that needed to be addressed and that widening access to other prescribers would go some way to resolving this but would result in increased usage.
- 1.3.4 The Committee considered that paediatric allergy was a specialised area but again, access to paediatric services remained an issue.
- 1.3.5 From a philosophical position, the Committee considered that given the evidence base for the general food supplements and that they are being used as a food replacement for many patients, serious consideration could be given to delisting these from the Pharmaceutical Schedule.

1.4 Neurological Subcommittee Minutes – 5 August 2010

- 1.4.1 The record of the meeting was noted and accepted.

2 Lacosamide (Vimpat) for treatment resistant epilepsy.

- 2.1 The Committee reviewed the Special Authority criteria previously recommended for lacosamide (Vimpat) for treatment-resistant epilepsy. The Committee considered that there should not be a requirement for three sodium channel blockers to be tried prior to accessing lacosamide, because the chance of success from a third sodium channel blocker after the failure of two prior sodium channel blockers is considered by neurologists to be very low. In addition, the Committee considered that highly treatment-resistant patients may only be taking one antiepilepsy treatment so there should not be a requirement for patients to be taking two antiepilepsy treatments in order to access lacosamide. Therefore, the Committee **recommended** the following changes (changes in ~~strikeout~~ and bold):

Initial application from any relevant practitioner. Approvals valid for 15 months for applications meeting the following criteria:

~~Both~~All of the following:

- 1 Patient has partial onset epilepsy; and
- 2 Seizures are not adequately controlled by, or patient has experienced unacceptable side effects from optimal treatment with all of the following: sodium valproate, ~~carbamazepine, phenytoin sodium, lamotrigine,~~ topiramate and levetiracetam **and any two of carbamazepine, lamotrigine and phenytoin sodium** (see Notes).; ~~and~~
- 3 ~~Patient is currently taking at least two antiepilepsy treatments.~~

Notes: "Optimal treatment" is defined as treatment which is indicated and clinically appropriate for the patient, given adequate doses for the patient's age, weight and other features affecting the pharmacokinetics of the drug with good evidence of compliance. Women of childbearing age are not required to have a trial of sodium valproate.

Renewal from any relevant practitioner. Approvals valid for 2 years where the patient has demonstrated a significant and sustained improvement in seizure rate or severity

and/or quality of life compared with that prior to starting lacosamide treatment (see Note).

Note: As a guideline, clinical trials have referred to a notional 50% reduction in seizure frequency as an indicator of success with anticonvulsant therapy and have assessed quality of life from the patient's perspective.

3 Azacitidine (Vidaza) for myelodysplastic syndromes

- 3.1 The Committee noted additional information from Celgene regarding PTAC's concerns from August 2010 that there may be potential bias in the AZA-001 azacitidine study due to loss to follow-up.
- 3.2 The Committee considered that the data provided showed a high number of patients were lost to follow-up and reiterated its previous **recommendation** that azacitidine should be funded on the Pharmaceutical schedule for the treatment of patients with intermediate-2 or high risk MDS, CMML or MDS-associated AML. The Committee gave this recommendation a low priority.

4 Varenicline (Champix) for smoking cessation

- 4.1 The Committee noted the request for clarification of the varenicline Special Authority from PHARMAC staff. The Committee reviewed whether the restriction "the patient has not used varenicline in the last 12 months" meant "the patient has not used *any* varenicline" or "the patient has not used *funded* varenicline".
- 4.2 The Committee considered that the intent of the Special Authority was that "the patient has not used funded varenicline in the last 12 months" and **recommended** that the wording of the Special Authority be amended to reflect this.

5 Benzbromarone for gout

Application

- 5.1 The Committee considered submissions from the New Zealand Rheumatology Association (NZRA) and the Maaori Gout Action Group, Counties Manukau DHB in support of the listing of benzbromarone on the Pharmaceutical Schedule for the treatment of gout. The Committee also considered additional information provided by PHARMAC staff in relation to benzbromarone.

Recommendation

- 5.2 The Committee **recommended** that benzbromarone be listed in the Pharmaceutical Schedule, subject to the following Special Authority criteria, with a high priority:

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

Both:

- 1 Any of

- 1.1 The patient has a serum uric acid level greater than 0.36 mmol/l despite treatment with allopurinol at doses up to at least 600 mg/day and appropriate doses of probenecid; or
- 1.2 The patient has experienced intolerable side effects from allopurinol such that treatment discontinuation is required and satisfactory control of serum uric acid (to less than 0.36 mmol/l) could not be achieved by probenecid; or
- 1.3 Both:
 - 1.3.1 The patient has renal impairment and serum uric acid remains greater than 0.36 mmol/l with an adjusted dose of allopurinol; and
 - 1.3.2 The patient has a rate of creatinine clearance >30 ml/min; or
- 1.4 The patient has had a renal transplant and requires urate-lowering therapy; and
- 2 The patient is receiving monthly liver function tests.

Renewal from any relevant practitioner. Applications valid for two years for applications meeting the following criteria:

Both:

- 1 The treatment remains appropriate and the patient is benefitting from treatment; and
- 2 There is no evidence of liver toxicity.

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; (vii) The direct cost to health service users.*

Discussion

- 5.3 The Committee noted that benzbromarone was first introduced in the 1970s. However, it is not registered for use in New Zealand and was withdrawn worldwide by the original supplier in 2003 following reports of serious hepatotoxicity. It is still marketed in several countries by other suppliers but is currently only available in New Zealand in small quantities imported under Section 29 of the Medicines Act by a specialist wholesaler. The Committee noted that there appears to be increasing support in the medical community for the use of benzbromarone in New Zealand, in particular for Māori and Pacific Island patients, and that Medsafe had indicated there was some potential for a supplier to gain registration for benzbromarone if a suitable product can be sourced and there is a demonstrated clinical need.
- 5.4 The Committee noted that gout is the most common inflammatory polyarthritis in men and that the incidence of gout worldwide is increasing. The Committee noted that the prevalence of gout among Pacific and Māori men is high (approximately 15% and 9%, respectively) compared to approximately 2% of Caucasian men. The Committee also noted that gout is potentially curable with normalising of uric acid.
- 5.5 The Committee noted that there are currently two fully funded urate-lowering treatments in New Zealand for the long-term management of gout: allopurinol (a xanthine oxidase inhibitor which inhibits production of urate) and probenecid (a uricosuric agent which promotes urate excretion from the renal tubules).
- 5.6 The Committee considered that allopurinol is generally well tolerated, with skin rash the most common side effect (in up to 2% of patients). However, it is associated with severe and life-threatening hypersensitivity reactions such as Stevens-Johnson syndrome and

toxic epidermal necrolysis. The incidence of these reactions from allopurinol is estimated to be approximately one in 56,000. People with renal impairment are considered to be at particular risk of the hypersensitivity reactions and lower doses of allopurinol are recommended in such patients. However, the Committee noted that findings from an observational study conducted in South Auckland suggests that dose adjustment based on creatinine clearance (CrCl) leads to suboptimal control of hyperuricaemia in the majority of patients treated with allopurinol (Dalbeth et al. *J Rheumatol* 2006;33:1646-50).

- 5.7 The Committee considered that probenecid is also generally well tolerated, with the key drawbacks being its propensity to cause nephrolithiasis and its lack of efficacy in patients with moderate to severe renal impairment.
- 5.8 The Committee noted that according to PHARMAC's data approximately 76,000 patients take allopurinol each year and 4,000 patients take probenecid. The Committee noted that it appeared from the data that some patients on allopurinol may be underdosed. The Committee considered that the relatively low use of probenecid and the low dosing of allopurinol suggest that the currently available agents are not optimally used in New Zealand. The Committee considered that there was increasing evidence to suggest that higher doses of allopurinol are more effective and may be used safely, noting that the Medsafe datasheet for allopurinol suggests that doses up to 900 mg/day can be used in patients with normal renal function.
- 5.9 The Committee noted that benzbromarone is a bezofuran derivative which increases urinary uric acid excretion in individuals with normal and high uric acid levels, via reduction in reabsorption of uric acid in the proximal tubule. The reabsorption of urate in the proximal tubule is maintained by a variety of transporter proteins. The Committee noted that variations in the gene for one of these transporters, the fructose transporter SLC2A9, may confer a particularly high risk for gout in Māori and Pacific Island peoples (Hollis-Moffat et al. *Arthritis Rheum* 2009;60:3485-92) and that benzbromarone, unlike probenecid, targets SLC2A9 (Caulfield et al. *PLoS Med* 2008;5(10)e197).
- 5.10 The Committee reviewed reports of several studies comparing benzbromarone with allopurinol or probenecid (Heel et al. *Drugs* 1977;14(5)349-66; Liang et al. *West China Medical Journal* 1994;9(4):405-8 [abstract only available in English]; Perez-Ruiz et al, *Ann Rheum Dis* 1998;57:545-549; Reinders et al. *Ann Rheum Dis*. 2009;68:51-56; Reinders et al. *Ann Rheum Dis*. 2009;68:892-7). The Committee considered that there was reasonable evidence to suggest that benzbromarone 100 mg/day is at least as effective as allopurinol ≥ 300 mg/day or probenecid 1 g/day in lowering serum urate levels, with a similar incidence of common adverse reactions.
- 5.11 The Committee considered that the open-label randomised controlled trial in which benzbromarone was compared with probenecid in patients who had previously tried allopurinol (either could not tolerate it or had not attained the target serum urate level) (Reinders et al. *Ann Rheum Dis*. 2009;68:51-56) provided moderate quality evidence in support of the efficacy of benzbromarone as a second-line treatment following allopurinol. In this study, benzbromarone 200 mg/day was found to be significantly more effective than probenecid 2 g/day after two months and was better tolerated. The Committee considered that this study was associated with a number of limitations, including small sample size, the use of supra-therapeutic doses and a relatively short-term follow-up.

- 5.12 The Committee reviewed three publications involving the use of benzbromarone in patients with renal impairment (Perez-Ruiz et al. *J Clin Rheumatol* 1999;5:49-55; Kumar et al. *NZ Med J* 2005;118:U1528; Masbernard et al. *S Afr Med J* 1981;59:701-6), noting that it was not possible to review two additional commonly cited studies (Ravera R. *Minerva Med* 1975;66:783-800; Didier & Olmer. *Sem Hop* 1987;54:463-5) because no English translation was available. The Committee considered that the quality of the available evidence was low to moderate, as it consisted of open-label and observational studies in small numbers of patients. The Committee considered that the evidence provided moderate support for the use of benzbromarone in patients with mild to moderate renal impairment; however, it was noted that the efficacy of benzbromarone appeared to decrease with reducing renal function and that higher doses (ie greater than 100 mg/day) may be needed in patients with CrCl less than 40 ml/min.
- 5.13 The Committee noted that there is a high incidence of gout in transplant patients, which is attributed at least in part to the use of cyclosporin in these patients. The Committee noted that while this can be managed using allopurinol in many cases, there is a significant drug-drug interaction between allopurinol and azathioprine (used in renal transplant patients) which can lead to a significant risk of potentially life-threatening agranulocytosis. The Committee noted that the Transplant Immunosuppressant Subcommittee considered that there was an unmet clinical need for a uric-acid lowering treatment for patients who suffered gout while taking cyclosporin and azathioprine. The Subcommittee had suggested that one option could be to reduce the azathioprine dose when administering allopurinol, but noted that the interaction was unpredictable and could have serious consequences for the patient. The Committee noted the Subcommittee's comment that the patient could be switched to a different immunosuppressant, for example mycophenolate; however, the Committee considered that switching treatments could be costly and problematic in some patients
- 5.14 The Committee noted that only one study investigating the use of benzbromarone in renal transplants had been identified (Zurcher et al. *Nephrol Dial Transplant* 1994;9:548-51). In this study, 25 cyclosporin-treated renal transplant patients with stable graft function and hyperuricaemia were given benzbromarone 100 mg/day for four weeks in addition to their established medication. Benzbromarone normalised plasma uric acid in 21 of the 25 patients. The remaining four patients had CrCl between 21 and 25 ml/min. Benzbromarone was well tolerated and cyclosporin trough values were not influenced by benzbromarone. The Committee considered that the study was of low quality and provided moderate support for the use of benzbromarone in renal transplant patients.
- 5.15 The Committee noted that four reports of hepatotoxicity with benzbromarone leading to death in two of the four patients led to its withdrawal in many countries by the original supplier in 2003. A review by Lee et al (*Drug Safety* 2008;31:643-665) reports 11 other cases resulting in nine deaths. The authors estimated the incidence of hepatotoxicity of benzbromarone to be around one in 17,000 and conclude that adverse events are relatively infrequent but potentially severe. The Committee agreed with the author's suggestion that probenecid should be used as the first uricosuric agent before trying benzbromarone, and that the risk of hepatotoxicity with benzbromarone could be reduced by employing a graded dosage increase together with regular liver function monitoring.
- 5.16 The Committee considered that if benzbromarone was funded it would largely be used as an add-on or single-agent treatment in patients with inadequate control from

allopurinol or who were intolerant to allopurinol. However, the Committee reiterated its view that it would be preferable to use probenecid in this patient population if possible.

- 5.17 The Committee considered that benzbromarone would most benefit patients requiring urate-lowering therapy who are intolerant to allopurinol, who have received inadequate response to allopurinol at higher doses, who have moderate renal impairment and who have had a renal transplant. The Committee considered that there was a high unmet clinical need in these patient populations, which include a high proportion of Māori and Pacific Island people.
- 5.18 The Committee considered that, given the significant cost differential between allopurinol and benzbromarone, it would be important to ensure that patients accessing benzbromarone following allopurinol have had a trial of allopurinol at higher doses, to ensure that the allopurinol failure was not simply a result of underdosing. The Committee also considered that, on the basis of the available evidence, it would be reasonable to try adding probenecid to allopurinol instead of switching to benzbromarone as a means to improve efficacy, providing that the patient had adequate renal function. Therefore, if there was a significant cost difference between benzbromarone and probenecid, and given benzbromarone has been associated with hepatotoxicity, it would be reasonable to include this as a requirement prior to accessing benzbromarone.
- 5.19 The Committee considered that the appropriate dosing schedule for benzbromarone would be 100 mg/day, which could be increased to 200 mg/day in cases of renal impairment or where serum uric acid remains high.
- 5.20 The Committee noted that there could be additional costs to the health sector associated with liver function monitoring, but considered that this could be outweighed by the benefits of reduction in disease burden.
- 5.21 The Committee considered that the PHARMAC staff estimates of patient numbers were reasonable (between 6,000 and 7,000 per year) but may be on the low side.

6 Dornase alfa for cystic fibrosis

Application

- 6.1 The Committee reviewed a proposal from the Cystic Fibrosis Advisory Panel for widening access to dornase alfa for patients with cystic fibrosis.

Recommendation

- 6.2 The Committee **recommended** that access to dornase alfa be widened for cystic fibrosis patients subject to the following Special Authority (changes in ~~strike through~~ and **bold**), with a medium priority:

Patients eligible for initiation a one month trial of domase alfa therapy.

~~Cystic fibrosis patients~~ **Patients with cystic fibrosis** who are eligible for an initial **one month** trial of ~~four weeks~~ of dornase alfa are those **who**:

- (a) **are** willing to undertake a trial of dornase alfa; **and**
- (b) **are aged** five years or older; **and**
- ~~(c) with FEV₁ less than 65% predicted (for age, gender and height);~~
- (c) ~~who~~ are clinically stable, as documented by three consistent (or stable) baseline measurements of FEV₁ and FVC within the six weeks prior to application; **and**
- (d) ~~who have evidence of chronic suppurative disease (cough and sputum most days of the week, or greater than three respiratory tract infections of more than two weeks' duration in any twelve months)~~ **have ongoing respiratory infections in keeping with cystic fibrosis; and**
- (e) **have previously undergone a trial with, or are currently being treated with, hypertonic saline; and**
- (f) ~~who~~ are provided with written acknowledgement of the nature of the trial of therapy and that continued treatment may not be recommended or made available; **and**
- (g) ~~be~~ **are** willing to continue with other standard treatments including secretion removal techniques, pancreatic enzyme supplements, vitamin supplements, etc.

This phase of initial therapy is limited to ~~four weeks'~~ **one month's** treatment with dornase alfa at a dose of 2.5 mg daily.

Immediately **before starting** ~~prior to instigation~~ of dornase alfa therapy, a further baseline measurement of FEV₁ and FVC (best of three measurements) should be undertaken. Only if continuing stability is demonstrated should the trial be commenced. If previous bronchial hyper-reactivity has been demonstrated it is recommended that respiratory function tests should always be ~~done~~ **performed** 10 to 15 minutes after treatment with a bronchodilator. Other lung volume measurements recorded in the previous 12 months should also be included in the application.

Continuation of therapy **Patients eligible for a six month trial of dornase alfa therapy**

At or towards the end of the initial ~~four weeks'~~ **one month** trial, patients must be reassessed and further lung function measurements be undertaken (test under conditions as above). To be eligible for ~~continued~~ **a six month trial of dornase alfa** treatment, the following criteria must be met:

- (a) patient is willing to continue with treatment (implying a lack of significant adverse effects and improved quality of life); and
- ~~(b) at least a 10% improvement in baseline FEV₁.~~
- (b) • **for patients with a baseline FEV₁ greater than 90% predicted, a 3% or greater improvement in FEV₁ from baseline; or**
• **for patients with a baseline FEV₁ between 65-90% predicted, a 5% or greater improvement in FEV₁ from baseline; or**
• **for patients with a baseline FEV₁ less than 65% predicted, a 7.5% or greater improvement in FEV₁ from baseline.**

Six month trials **Patients eligible for long term dornase alfa therapy**

It is important that other aspects of treatment, such as physiotherapy, be continued. Following an initial six months therapy, a further assessment should be undertaken.

To be eligible for ~~continued treatment~~ **long term therapy**, the following criteria must be met:

- (a) Patient ~~is~~ **is** willing ~~ness~~ to continue with treatment. This requires a format assessment by the physician that in their opinion, and in the opinion of the patient (or the patient's family, in the case of paediatric patients), that ~~DNase~~ **dornase alfa** is continuing to produce worthwhile benefits. Such an assessment should include serial lung functions taken during the trial on at least 3 occasions i.e. 2 ½, 4 ½ and 6 months, impact on hospitalisation, infective exacerbations, antibiotic use etc.

- ~~(b) Dornase alfa therapy should cease if there is not general agreement of benefit, as there is always the possibility of harm from unnecessary use.~~
- ~~(c) Maintenance of FEV₁ at greater than or equal to 7.5% above original baseline.~~
- (c) • **for patients with a baseline FEV₁ greater than 90% predicted, maintenance of FEV₁ at greater than or equal to 3% above original baseline; or**
- **for patients with a baseline FEV₁ between 65-90% predicted, maintenance of FEV₁ at greater than or equal to 5% above original baseline; or**
- **for patients with a baseline FEV₁ less than 65% predicted, maintenance of FEV₁ at greater than or equal to 7.5% above original baseline.**

Dornase alfa therapy should cease if there is not general agreement of benefit, as there is always the possibility of harm from unnecessary use.

Long term Treatment dornase alfa therapy

After completion of ~~the~~ **a successful** six month trial, patients are eligible for continuation on long term therapy, **which is reviewed annually.**

To be eligible for ~~continued treatment,~~ **long term therapy**, the following criteria must be met:

- (a) **patient is willing and consents to continue with treatment** ~~patient consent and willingness to continue with treatment is required.~~ This requires a formal assessment by the physician that in their opinion, and in the opinion of the patient (or the patient's family, in the case of paediatric patients) that ~~DNase~~ **dornase alfa** is continuing to produce worthwhile benefits. Such an assessment should include impact of hospitalisation, infective exacerbations, IV antibiotic use, outpatient visits, height, weight etc; **and**
- (b) serial lung functions ~~taken~~ **testing** at 3-monthly intervals and regular reviews by physician; **and**
- (c) ~~provision of the formal assessments and lung function tests~~ **are provided** to the Cystic Fibrosis Advisory Panel. **This** is a requirement ~~for~~ **of** continued supply. **Patients will also be asked to consent to** ~~A request would be made asking the patient to allow~~ **this information being** included in the national CF database.

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 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.*

- 6.3 The Committee had further **agreed** to send a letter to the New England Journal of Medicine requesting corrections to the publication by Fuchs et al (NEJM 1994;331:637-64), to publicise errors that had affected previous eligibility-setting for dornase alpha in New Zealand.

Discussion

- 6.4 The Committee noted that there is good evidence to show that life expectancy of cystic fibrosis patients has increased over the past 40 to 50 years. In the 1960s very few children with the disease reached school age, but at present the average life expectancy

is approximately 38 years (Patient Registry, Annual Data Report 2008, U.S. Cystic Fibrosis Foundation).

- 6.5 The Committee also noted that the median predicted FEV₁ percentage has increased from 86% at age 6 in 1983 to 95% in 2008 (Canadian Cystic Fibrosis Patient Data Registry Report, 2008). The proportion of patients with cystic fibrosis over the age of 18 years has also increased from 28% in 1983 to 57% in 2008 (Canadian Data). The reasons for the improvement include better nutrition, physiotherapy, antibiotics together with the realization that there are patients with mild disease (when the pancreas is not involved) and some patients are only diagnosed in adulthood.
- 6.6 The Committee noted that, while the absolute role of dornase alfa is not known, it does reduce admissions to hospital and preserves respiratory function.
- 6.7 Members noted the results from a recent Cochrane Review (Jones AP, Wallis C. Dornase alfa for cystic fibrosis. Cochrane Database of Systemic Reviews 2010, Issue 3. Art.No.:CD001127). The review's search included 43 trials, of which 15 met inclusion criteria with a total of 2,469 patients. Twelve of the studies compared dornase alfa with placebo or no dornase alfa treatment, one compared daily dornase alfa with hypertonic saline to alternate day dornase alfa, and two compared dornase alfa with hypertonic saline. There were no differences in the number of deaths between treatments, but an improvement in spirometry was seen in the treated groups for up to two years; however, one study showed no difference over three years. Improvement in spirometry levels was seen by week two in some studies and definitely by one month. Dornase alfa treatment was associated with voice alteration and rash. Results of the studies were recorded as change in FEV₁, respiratory exacerbations and quality of life.
- 6.8 The Committee noted that the percentage change in predicted FEV₁ varied between trials and that there is a need for long term studies in children to evaluate the effect on FEV₁.
- 6.9 The Committee noted that the Quan paper (Quan et al, J Paediatr 2001; 139:813-20) used an inclusion criteria of >85% FVC predicted and that the Cystic Fibrosis Advisory Panel had recommended that the upper inclusion level for the six month trial and long term treatment be set at >90% FEV₁ predicted. In recommending that the six month review should remain, members noted that this is the usual practice in many countries and is good medical practice.
- 6.10 The Committee noted the response from Roche, regarding the PHARMAC letter that questioned the reported baseline FEV₁ data in a pivotal trial (Fuchs et al. NEJM 1994;331:637-64). This data had informed the setting of the current eligibility criteria for access to dornase alpha. In its response Roche agreed that the Fuchs publication had reported data that was incorrect, and provided the corrected data. The Committee considered that this was an important issue relevant to other settings that needed to be publicised, and that the New England Journal of Medicine should be asked to publish a correction.
- 6.11 For the record, the specific problem that PHARMAC and PTAC had identified related to the previous setting of eligibility criteria that used an FEV₁ threshold of less than 65% predicted. This was where eligibility-setting had been based on the reported baseline mean FEV₁ % of predicted plus one standard deviation across the three groups in the

Fuchs et al study population as published. However, on review, two of the published standard deviation values had appeared to be inaccurate by a factor of 10, and Roche now advised that indeed the baseline standard deviation values for FEV₁ % predicted in two of the three groups in the study had been reported incorrectly. The correct mean FEV₁ % of predicted and one standard deviation values in the three groups in the trial were 61.0 +/- 25.2 for the Placebo group, 61.1 +/- 26.9 for the rhDNase once daily group, and 60.0 +/- 26.9 for the rhDNase twice daily group. The corrected standard deviations translate to mean FEV₁ % predicted plus one standard deviation values between 86% and 88% of predicted.

- 6.12 The committee noted the results of the CUA and gave advice on clinical aspects to further update the CUA.

7 Rifabutin (Mycobutin) for refractory helicobacter pylori treatment

Application

- 7.1 The Committee reviewed an application from the New Zealand Society of Gastroenterology for the use of rifabutin (Mycobutin) on the Pharmaceutical Schedule for the treatment of refractory helicobacter pylori.

Recommendation

- 7.2 The Committee **recommended** that the current listing of rifabutin, restricted by the 'Specialist' requirement in the Pharmaceutical Schedule, should remain unchanged, as the listing was appropriate and allows rifabutin to be used in patients with helicobacter pylori.

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.*

Discussion

- 7.3 The Committee considered the evidence for efficacy of rifabutin in *H. pylori* infection to be of moderate quality as the trials did not involve large patient numbers. Members noted the Borody et al paper (Alimentary Pharmacology and therapeutics, 2006; 23 :481-488) and Van der Poorten & Katelaris paper (Alimentary Pharmacology and therapeutics, 2007; 26 :1537-1542) which both showed that rifabutin in combination with a proton pump inhibitor and amoxicillin had good efficacy in treating patients who had failed first line *H. pylori* eradication therapy.
- 7.4 The Committee considered that the 29% failure rate suggested in the Borody et al paper was probably higher than would be found in clinical practice as patients treated with

primary therapy for *H. pylori* did not routinely undergo 14 C-urea breath testing to ensure eradication. Members considered that patients who failed to respond to first line therapy and continued to exhibit symptoms would be referred to a gastroenterologist for further diagnosis and treatment.

- 7.5 The Committee noted that there was a risk of toxicity associated with rifabutin. Members considered that there was a small risk of tuberculosis resistance developing with increased usage of rifabutin. However, given New Zealand's low rate of tuberculosis this may not be as relevant as in high tuberculosis prevalent countries.
- 7.6 The Committee noted that with the discontinuation of bismuth compounds and tetracycline there were no second line therapies available for patients with resistant *H. pylori*. Members noted that PHARMAC had included levofloxacin in the 2010/11 Tender. Members considered that if levofloxacin was available that this product would be preferred to rifabutin for resistant *H. pylori*.
- 7.7 Members noted that rifabutin was currently restricted by the 'Specialist' requirement in the Pharmaceutical Schedule. The Committee noted that currently gastroenterologists could prescribe funded rifabutin for resistant *H. pylori*. Members considered there was no clinical requirement to further restrict rifabutin.

8 Imiglucerase (Cerezyme) for Type 1 and Type 3 Gaucher disease

Application

- 8.1 The Committee considered an Application from the Gaucher Panel to widen access to imiglucerase for the treatment of Gaucher Disease in children via the Gaucher Panel.

Recommendation

- 8.2 The Committee **recommended** that access to imiglucerase for treatment of children with Type 1 and Type 3 Gaucher disease be widened, under the existing Panel Access, to include a maximum dose of 30 iu per kg per month for children with Type 1 and Type 3 Gaucher Disease who do not achieve the appropriate biological markers on a dose of 15 iu per kg per month.

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.*

- 8.3 The Committee further **recommended** that the Gaucher Panel develop criteria that provide documented clinical endpoints to assess adequacy/inadequacy of response to therapy for allowing dose amendments.

Discussion

- 8.4 The Committee noted that imiglucerase was funded for the treatment of Type 1 Gaucher Disease to a maximum of 15 iu per kg per month on application to the Gaucher Panel for patients meeting the entry criteria. Members noted that three patients with Type 1 Gaucher Disease had increased doses (up to 30 iu per kg per month). Members noted that two Type 3 Gaucher disease patients had been funded via the Community Exceptional Circumstances scheme with doses greater than 30 iu per kg per month.
- 8.5 The Committee considered that the quality of the evidence was poor; however, the Committee noted that this was a rare disease and there were unlikely to be large randomised controlled trials.
- 8.6 The Committee noted the Goldblatt et al paper (Internal Medicine J, 2005; 35:156-161) a prospective follow up study of patients treated with enzyme replacement therapy (ERT) in Australia. Members noted that the process for ERT funding in Australia also involved a panel of clinicians with expertise in metabolic medicine, genetics and haematology. Members noted that dose levels were not provided separately for children. Members noted that the mean starting dose was 60 iu per kg per month and the mean maintenance dose was also 60 iu per kg per month. Members noted that there was improvement in haemoglobin and platelet levels and a reduction in spleen and liver volume in the majority of patients.
- 8.7 The Committee noted the Brunel-Guitton et al paper (Molecular genetics and metabolism, 2009; 96:73-76) a retrospective review of nine patients in one centre. Members noted that the median age of initiation was 5.7 years and the average dose of imiglucerase at initiation was 78 iu per kg per month. Six out of nine patients received maintenance doses of 30 – 37 iu per kg per month for a median period of four years. All patients bar one maintained therapeutic goals.
- 8.8 The Committee noted the Kesselman et al paper (Blood cells, Molecules, and Diseases, 2006; 37:46-49) a description of the current funding situation of imiglucerase in Israel. Israel has an increased burden of Gaucher Disease due to high prevalence of Ashkenazi Jews. Members noted that 184 patients received a dose of 30 iu per kg per month. Members noted that this dose was recommended for patients with Type 3 (neuronopathic disease) Gaucher Disease to treat non-neuronopathic signs and symptoms. Members noted that the paper provided no evidence to support the clinical effectiveness of the protocol.
- 8.9 Members noted the Altarecu et al paper (J of Pediatrics, 2001; 138:539-547) a prospective cohort study of 21 Type 3 Gaucher Disease patients receiving ERT. 18 patients received initiation doses of 120 iu per kg per month with the remaining three receiving higher doses. Four patients died during the study. Maintenance dose was 120 iu per kg per month for all but three patients. Treatment resulted in improvement in haematological, bone, liver and splenic parameters. At the end of the follow up there was no change in pulmonary interstitial disease and no change in IQ scores but eight out of 21 patients had neurological deterioration.
- 8.10 Members noted the Cox-Brinkman et al paper (J Inherit Metab dis, 2008) a case report of three siblings with Gaucher Disease Type 3. Two of the siblings received very high dose ERT followed by miglustat after 10 and seven years on ERT. Both showed severe neurological deterioration from 1.5 years. The 3rd sibling received imiglucerase at 240 iu per kg per month plus miglustat from 5 months of age. At 3.5 years of age the child

appeared developmentally normal. Members noted the short follow-up period and the fact that phenotypes can vary considerably within families.

- 8.11 Members noted the Davies et al paper (J Inherit Metab Dis, 2007; 30:935-942) which reported on 55 cases of Type 3 Gaucher Disease who received ERT. The study noted there was a large variation of dose of ERT reported with older patients using lower doses and younger patients using higher doses (approximately 240 iu per kg per month). The paper provided no evidence that very high doses had benefit with eight years follow up. The Committee noted an accompanying commentary from Zimran and Elstein (J. Inherit Metab Dis. 2007; 30:843-844) which recommended that ERT for Type 3 Gaucher Disease should be for visceral disease, with a usual dose between 30 and 60 iu per kg per month.
- 8.12 The Committee noted the tabled updated PHARMAC cost-utility analysis of increasing the dose of imiglucerase in poorly controlled patients with Type 1 Gaucher Disease. Members noted that the cost per QALY was estimated to be between cost-saving and \$310,000.
- 8.13 The Committee noted the ongoing supply problems due to supplier manufacturing difficulties. Members noted this was particularly problematic as New Zealand utilised a significantly lower dose than other countries.
- 8.14 The Committee noted the March 2010 Gaucher Panel minutes. Members noted that the Panel considered the current low dose of imiglucerase for adults to be appropriate.
- 8.15 Members noted that the Panel considered that children who present at a young age with Type 1 or Type 3 Gaucher Disease are likely to need a higher starting dose of 30 iu per kg per month. Members noted that the Gaucher Panel requested the ability to initiate children only (not adults) on a dose of 30 iu per kg per month.
- 8.16 Members noted that the population of patients with Gaucher Disease was small in New Zealand and that there had been no new patient's initiated on therapy since 2007. Members noted that imiglucerase was very expensive and that allowing an increased dose would be a fiscal issue.
- 8.17 Members considered it to be appropriate to initiate therapy on a dose of 15 iu per kg per month and allow this to increase to 30 iu per kg per month should a child fail to show improvement in haematological, bone, liver and splenic parameters. Members also considered that the Gaucher Panel should develop criteria for assessing response to therapy that would be assessed by the panel prior to approving an increased dose. The Panel should further develop a protocol for dose reduction.

9 Miglustat (Zavesca) for mild to moderate Type 1 Gaucher disease

Application

- 9.1 The Committee considered an Application from Actelion Pharmaceuticals Pty Ltd for funding of miglustat for mild to moderate Gaucher Disease in Adults.

Recommendation

- 9.2 The Committee **recommended** that miglustat be funded for the treatment Type 1 Gaucher disease via the Gaucher Panel, for patients who are refractory to imiglucerase or show toxicity to imiglucerase or who are unable to comply with imiglucerase regimen with a low priority.

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;* *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

- 9.3 The Committee noted that substrate reduction therapy (SRT) was a new treatment strategy for Gaucher Disease. Members noted that miglustat is a glucosylceramide synthase inhibitor, which was intended to reduce the level of substrate enough to allow residual activity of the deficient enzyme to be effective. Members noted that miglustat is approved for mild to moderate substrate reduction in Type 1 Gaucher Disease. Members noted that the standard dose for miglustat is 100 mg three times daily.
- 9.4 Members noted that the most common side effects are gastro-intestinal which affect up to 80% of patients, with patients also reporting tremor and weight loss. Members noted that diarrhoea was the most common side effect but considered that with dietary advice around reducing disaccharide intake this could be reduced. Dose reduction was also noted as a method to reduce diarrhoea. Members noted that peripheral neuropathy was also reported however as this was recognised as a symptom of Gaucher Disease it was difficult to determine causation.
- 9.5 The Committee noted that approximately 15% of patients treated with imiglucerase develop IgG antibodies to it, leading to hypersensitivity reactions. Members noted that the risk of anaphylaxis was low. Members noted that approximately 50% of patients experience adverse events with imiglucerase with around 3% discontinuing due to severity Beutler and Grabowski 2001 (*The Metabolic and Molecular Bases of Inherited Disease* 8th edition; 3635-3668)
- 9.6 Members considered the evidence to be of poor to moderate quality but noted that Gaucher Disease was rare and large randomised controlled trials were unlikely in this patient population. Members noted there was little direct evidence to support the supplier's indications for miglustat reimbursement in their application.
- 9.7 The Committee noted the Elstein et al paper (Blood, 2007; 110: 2296-2301) a randomised open label phase II study comparing miglustat, miglustat with imiglucerase and imiglucerase alone. 36 adult patients with Type 1 Gaucher Disease who had been stabilised on imiglucerase for at least two years were randomised to each intervention group for six months. Following this all patients entered into an open label extension of miglustat monotherapy. At six months there was no difference in liver and spleen size or haemoglobin and platelet count. There was a possible improvement in quality of life as determined by SF36 in the miglustat group. Treatment with miglustat alone was

considered to be more convenient by participants. Safety data after two years showed that 94% of participants reported diarrhoea, 35% tremor and 82% weight loss.

- 9.8 The Committee noted the Cox et al paper (The Lancet, 2000; 355: 1481-85) an open label study of 28 participants with Type 1 Gaucher disease unwilling or unable to receive imiglucerase. After 12 months of miglustat treatment liver volume was reduced by 12% and spleen volume by 19%. Six patients withdrew over the year, with two due to gastrointestinal side-effects. Two further patients withdrew at the end of the 12 month period because they developed peripheral neuropathy. At a 36 month open label extension follow up (Elstein et al, J. Inherit. Metab. Dis, 2004; 27:757-766), visceral and histological markers had continued to statistically improve, with liver volume reducing by 17% and spleen volume by 29.6%.
- 9.9 The Committee noted the Pastorers et al paper (Clinical therapeutics, 29; 2007:1645-1654) a pooled analysis of 72 patients receiving miglustat 100 mg three times daily. DEXA was recorded at baseline, 6, 12 and 24 months. BMDz scores improved at all times points for lumbar, spine and femoral neck. 83% of the 65 patients with bone pain at baseline reported no pain at two years.
- 9.10 The Committee noted the Hollak et al paper (Pharmacoepidemiology and drug safety, 2009) which was a five year post authorisation safety report. 68% of patients had previously received imiglucerase. New tremor was reported in 12.3% of patients, existing tremor worsened in 3.3% of patients and 3.3% had new peripheral neuropathy. 35 discontinued treatment; 21 due to adverse events, three to disease progression and one to non-compliance.
- 9.11 Members considered that miglustat may replace imiglucerase in Type 1 patients with mild to moderate disease who were refractory to imiglucerase or had toxicity or were unable to comply with the regimen. Members noted that miglustat was an oral therapy and there would be a benefit as patients would no longer require fortnightly infusions.
- 9.12 The Committee considered that miglustat should not be used in combination with imiglucerase as there was no evidence for increased efficacy of this combination therapy. Members noted that the availability of miglustat may aid in the ongoing treatment of patients when there is a short supply of imiglucerase.
- 9.13 The Committee considered there was no clinical reason not to list miglustat, but noted that the price of imiglucerase should be considered when considering a listing and that the cost should be calculated on a dose of 100 mg three times daily.

10 Voriconazole (Vfend) for invasive aspergillus and resistant candidiasis

Application

- 10.1 The Committee considered a PHARMAC Staff Proposal for voriconazole for invasive aspergillus and resistant candidiasis.

Recommendation

- 10.2 The Committee **recommended** that voriconazole be listed for invasive aspergillus and resistant candidiasis with a high priority.

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.*

- 10.3 The Committee further **recommended** that PHARMAC staff approach haematologists to define Special Authority criteria for these indications.

Discussion

- 10.4 The Committee considered that aspergillus treatment was complex and the issues were wider than individual patient risk factors. Members noted that invasive aspergillus was still associated with very high 30 to 50% mortality rate.
- 10.5 Members noted that voriconazole is an effective antifungal with up to 60 fold lower minimum inhibitory concentrations for *Candida* species (including resistant strains) than fluconazole. Members noted that voriconazole is fungicidal for aspergillus and has some activity against *Fusarium* species and *Scedosporium apiopermum*. Members noted that voriconazole is not active against Zygomycetes compared with amphotericin B.
- 10.6 Members noted the Herbrecht et al study (The New England Journal of Medicine, 2002; 347:408-415), a randomised unblinded trial comparing voriconazole with amphotericin B for primary therapy of definite or probable invasive aspergillus in immunocompromised patients. It was noted that voriconazole was associated with a higher response and survival rate at week 12, although there were issues with study design that may have biased the results in favour of voriconazole.
- 10.7 Members noted that PHARMAC had undertaken a cost-utility analysis (CUA) in 2003 for DHB hospitals on voriconazole for invasive aspergillus. It was noted that the analysis determined that voriconazole was not relatively good value for money compared with amphotericin B when used as first line therapy for proven or probable invasive aspergillus infection. Members noted that standard treatment in New Zealand had changed in recent years, with standard treatment now consisting of liposomal amphotericin B, caspofungin or voriconazole; or combinations of these products. It was noted that standard amphotericin B was rarely used in many haematological services due to the higher rates of nephrotoxicity and other side effects.
- 10.8 The Committee noted that there have been no clinical trials comparing the efficacy of voriconazole with liposomal amphotericin or caspofungin for the treatment of invasive aspergillosis.
- 10.9 Members noted that voriconazole was extensively used in the hospital setting in New Zealand but that discharge to the community required Hospital Exceptional

Circumstances applications. Members considered that the currently funded antifungals in Section B of the Pharmaceutical schedule, itraconazole and fluconazole, do not have the same efficacy or activity for the treatment of invasive aspergillus. It was noted that patients are often initiated on IV treatment and switch to oral treatment at a reasonably early stage, therefore allowing earlier discharge from hospital.

- 10.10 Members noted the difficulty in defining invasive aspergillus, as treatment could be initiated following a diagnosis of definite, probable, or possible invasive aspergillus. Members considered that a number of hospitals had protocols where antifungal therapy could be initiated when a patient had febrile neutropenia episode with no response over 72 hours to broad spectrum intra-venous antibiotics. Members noted that high resolution computed tomography (HRCT) and galactomanin testing were further diagnostic tools which could be considered when initiating antifungal therapy.
- 10.11 The Committee considered that voriconazole should also be considered for invasive candidiasis where there is proven resistance.
- 10.12 The Committee considered that haematologists were the specialty most likely to initiate voriconazole therapy in immunocompromised patients, and that PHARMAC staff approach haematologists to develop Special Authority eligibility criteria.

11 Posaconazole (Nofaxil) for prophylaxis of invasive aspergillus

Application

- 11.1 The Committee considered a PHARMAC Staff Proposal for posaconazole for prophylaxis of invasive aspergillus in immunocompromised patients.

Recommendation

- 11.2 The Committee **deferred a recommendation** for listing posaconazole, pending further information on current practice in the New Zealand setting.

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.*

- 11.3 The Committee further **recommended** that PHARMAC staff approach haematologists to assess current practice relating to posaconazole for prophylaxis of invasive aspergillus.

Discussion

- 11.4 The Committee considered that aspergillus prophylaxis was complex and the issues were wider than individual patients and the underlying immunocompromising condition. Members noted that filtration of ward facilities to reduce airborne exposure to aspergillus is important to reduce the incidence of fungal disease in immunosuppressed populations.

Members noted that invasive aspergillus is still associated with a high 30 to 50% mortality rate and that prevention of the condition is now possible.

- 11.5 The Committee noted the Cornely et al paper (The New England Journal of Medicine, 2007; 356: 348-359) which found that posaconazole appeared to provide additional benefit for prophylaxis over fluconazole and itraconazole. Members noted that the number needed to treat (NNT) to avoid one case of invasive fungal infection was 16 in the setting of neutropenia. Members noted the NNT would be dependant on environmental factors in individual hospitals as well as specific patient risk factors.
- 11.6 The Committee noted that patients who had acute myeloid leukaemia (AML) and stem cell transplants were at the patients with the highest risk of developing invasive aspergillus and would be a patient population that may benefit from posaconazole depending on environmental factors. Members considered that patients with acute lymphoblastic leukemia (ALL) were less likely to develop invasive aspergillus and that fluconazole was likely to be sufficient for this patient group.
- 11.7 The Committee noted that Hospital Exceptional Circumstances (HEC) had approved 22 of 28 applications for posaconazole for prophylaxis or treatment of invasive fungal infection, mainly in patients with AML undergoing chemotherapy and stem cell transplant patients with graft versus host disease.
- 11.8 Members considered that it may be appropriate to limit posaconazole prophylaxis to the first cycle of chemotherapy when the risk of invasive aspergillus is greatest. This strategy however has not been tested in clinical trials. It was noted that fluconazole is effective for those at lower risk of invasive aspergillosis.
- 11.9 The Committee considered that there was insufficient information regarding current clinical practice in New Zealand to make a recommendation. The Committee considered that PHARMAC approach haematologists around New Zealand to gain an understanding of current prophylactic treatment for invasive aspergillus.

12 Dabigatran (Pradaxa) for stroke, systemic embolism, atrial fibrillation

Application

- 12.1 The Committee considered an Application from Boehringer Ingelheim NZ Limited to fund dabigatran for prevention of stroke, systemic embolism and reduction of vascular mortality in patients in atrial fibrillation.

Recommendation

- 12.2 The Committee **recommended** that dabigatran be funded with low priority for prevention of stroke, systemic embolism and reduction of vascular mortality in atrial fibrillation.

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; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.

Discussion

- 12.3 The Committee noted that dabigatran is registered in New Zealand, and was previously reviewed by PTAC in November 2008 for the prevention of venous thromboembolism (VTE) following total hip and knee replacement, but is not currently registered for use in atrial fibrillation. The Committee noted that dabigatran was recently reviewed by the Cardiovascular Subcommittee for this indication, but the minutes were not yet available.
- 12.4 The Committee noted the pivotal study for dabigatran in atrial fibrillation, the RE-LY study (Connolly et al NEJM 2009; 361: 1139-1151), which was a randomised trial comparing two fixed doses of dabigatran, 110mg or 150mg twice daily administered in a blinded manner, and open label warfarin in patients with atrial fibrillation. The Committee noted that in the warfarin group, the mean percentage of the study period during which the International Normalised Ratio (INR) was within the therapeutic range was 64%. The Committee noted the rates of stroke or systemic embolism, which was the primary outcome, were 1.69% per year in the warfarin group compared with 1.53% per year in the 110mg dabigatran group and 1.11% per year in the 150mg dabigatran group. Both doses of dabigatran were non-inferior to warfarin ($p < 0.001$), and the 150mg dose of dabigatran was superior to warfarin with an absolute risk reduction (ARR) of 0.58% and number-needed-to-treat (NNT) of 172.
- 12.5 The Committee noted that the primary safety outcome of major bleeding in the RE-LY trial was lower with both dosages of dabigatran and was statistically significant for the 110mg dose (2.71% versus 3.36% per year, $p = 0.003$, ARR 0.65%, NNT 154). The Committee noted that the rate of gastrointestinal bleeding was significantly higher with the 150mg dabigatran dose than warfarin (1.51% versus 1.02% per year, ARR 0.49%, NNT 204), but intracranial haemorrhage was significantly lower with both dosages of dabigatran. The incidence of haemorrhagic stroke was significantly lower for both dosages of dabigatran when compared with warfarin, but the incidence of myocardial infarction was higher in the dabigatran groups ($p = 0.048$). The Committee noted that the mortality rate from any cause was not statistically different between the three treatment arms. The Committee noted that the net clinical benefit outcome, which was a composite measure of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death or major bleeding, was better with both dosages of dabigatran but that this was only statistically significant for the 150mg dabigatran dose ($p = 0.04$). The Committee noted that unlike ximelagatran, which was withdrawn from the market because of hepatotoxicity, no signal of hepatotoxicity was detected with dabigatran. The Committee considered that dyspepsia was however more common with dabigatran when compared with warfarin ($p < 0.001$).
- 12.6 The Committee considered that based on the RE-LY trial, the absolute risk reduction with dabigatran when compared with warfarin, although statistically significant, was very small (ARR 0.58%). Therefore, the Committee considered that dabigatran should be considered therapeutically equivalent to warfarin. The Committee also considered that

the evidence for increased safety of the 110mg twice daily dose of dabigatran for patients aged >75 years of age, or with creatinine clearance 30-50ml/min, with concomitant p-glycoprotein inhibitors or previous gastrointestinal haemorrhage, is inadequate.

- 12.7 The Committee also considered that the inability to monitor dabigatran therapy could mean that the first sign of over anticoagulation could be a major haemorrhage, especially in the elderly and those with renal impairment. There is also currently no antidote for dabigatran in the event of haemorrhage. The Committee noted that patients with a creatinine clearance of <30ml/min were excluded from the RE-LY trial. The Committee also considered that there are potentially significant drug interactions between dabigatran and p-glycoprotein inhibitors, with a risk of severe bleeding, and that possible interacting drugs are likely to include more than just verapamil, amiodarone and quinidine.
- 12.8 The Committee considered that although one of the advantages of dabigatran is its ease of use, it is noteworthy that the rates of discontinuation in the RE-LY trial were about 5% higher with dabigatran when compared with warfarin. Dyspeptic symptoms may also be a significant issue in real life practice. The Committee also considered that, due to its short half-life (unlike warfarin), missing a dose of dabigatran could be associated with an increased risk of stroke.
- 12.9 The Committee noted that there was no direct head-to-head trial comparing dabigatran with aspirin. The Committee noted the meta-analysis by Hart et al (Ann Intern Med 1999; 134:492-501) and the BAFTA study (Mant et al Lancet 2007; 370:493-503), which compared the efficacy of warfarin versus aspirin in atrial fibrillation. The BAFTA study indicated that warfarin resulted in an absolute risk reduction of 2.0% when compared with aspirin. The Committee was however concerned about making an indirect comparison and considered that evidence for dabigatran was currently lacking in patients who currently use aspirin because warfarin is contraindicated or maintaining INRs within the therapeutic range is difficult. This patient group was not included in the RE-LY trial. The Committee considered that although clinical evidence is currently lacking, this patient group would possibly benefit most from dabigatran.
- 12.10 The Committee noted that dabigatran was significantly more expensive than warfarin even after taking into account the cost of warfarin monitoring. The Committee considered that on average, patients stable on warfarin are tested every four to six weeks.
- 12.11 The Committee noted the supplier's recommendation to limit dabigatran to patients with CHADS₂ score ≥ 2 and who were contraindicated to warfarin or had trialled warfarin but INR levels failed to be maintained within the therapeutic range. The Committee considered that it would be difficult to restrict dabigatran use to certain subgroups of patients with atrial fibrillation without a significant risk of other patients with atrial fibrillation gaining access.
- 12.12 The Committee noted that although there are potential advantages of an oral anticoagulant like dabigatran that does not require regular monitoring, the main issue with dabigatran is its high cost and the risk of it being used in other patient groups beyond the funded indications. The Committee also considered that home INR testing of warfarin is currently being trialled and could reduce some of the burden of warfarin monitoring. The Committee noted that there are a number of other similar oral

anticoagulants, namely rivaroxaban and apixaban, which may present for funding, and resulting competition may result in price reductions.

13 Bortezomib for AL amyloidosis

Application

- 13.1 The Committee reviewed an application from [withheld under s9(2)(a) of the OIA] for the listing of bortezomib (Velcade) on the Pharmaceutical Schedule for the treatment of patients with systemic AL amyloidosis.

Recommendation

- 13.2 The Committee **recommended** that the application be deferred until Phase III trial data is available.

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

- 13.3 The Committee noted that the application was prompted by a review of Cancer EC applications conducted by the Cancer Treatments Subcommittee of PTAC (CaTSoP) at its November 2009 meeting.
- 13.4 The Committee noted that AL amyloidosis was a rare disease characterised by clonal expansion of plasma cells that affected approximately 30-40 New Zealanders per annum. Members further noted that the clinical manifestations of the disease were related to the accumulation of amyloid protein made up of light chains of immunoglobulin in the organs, most commonly cardiac failure, renal failure and nephrotic syndrome and peripheral neuropathy, and such organ involvement makes the treatment of AL amyloidosis with chemotherapy difficult. Members noted that the median survival for patients with AL amyloidosis is approximately 8-12 months, with longer survival in patients who undergo stem-cell transplantation (median survival of approximately four years).
- 13.5 The Committee noted that there are underlying similarities between AL amyloidosis and multiple myeloma; therefore the treatment regimens for AL amyloidosis were based on those developed for multiple myeloma. Members considered that currently most patients with AL amyloidosis in New Zealand would be treated with melphalan and high dose glucocorticoids (prednisone or dexamethasone) with or without stem cell transplantation. However, in patients where these treatments failed, treatment options are limited and members noted that thalidomide, whilst funded for the second line treatment of patients with multiple myeloma, was not funded for AL amyloidosis.

- 13.6 The Committee considered that there was a high unmet need for effective treatment options for patients with AL amyloidosis, and current treatments were unsatisfactory.
- 13.7 The Committee noted that rapid reduction in the level of light chains in patients with AL amyloidosis may be an important part of treatment, and that the rapid response associated with bortezomib may be an advantage.
- 13.8 The Committee noted that both PTAC and CaTSoP had reviewed the funding of bortezomib for multiple myeloma on a number of occasions. Members noted that bortezomib is indicated, in combination with melphalan and prednisone, for the treatment of patients with previously untreated multiple myeloma, who are not suitable for high dose chemotherapy and the treatment of multiple myeloma patients who have received at least one prior therapy, and who have progressive disease. However, bortezomib is not indicated for the treatment of patients with amyloidosis.
- 13.9 The Committee reviewed evidence from a number of studies. Members considered that, although the preliminary data appeared promising, the evidence for the use of bortezomib in AL amyloidosis was weak and of poor quality. Members noted that there were no randomised controlled studies examining the use of bortezomib in AL amyloidosis, and that studies in this patient group were limited to small single arm cohort studies. In addition, the Committee noted that there was no evidence available on the efficacy of bortezomib in treatment-naïve patients with AL amyloidosis.
- 13.10 The Committee considered that there was insufficient evidence at this time for it to conclude that bortezomib offered any advantage over other treatments in patients with AL amyloidosis, especially treatment naïve patients. Members noted that a phase III study, comparing oral melphalan plus dexamethasone with or without bortezomib in patients with amyloidosis, was currently recruiting patients overseas, and considered that it should review evidence from this study prior to making a recommendation for funding.

14 Lapatinib for metastatic breast cancer

Application

- 14.1 The Committee reviewed an application from The New Zealand Association of Cancer Specialists – Breast Special Interest Group (BSIG) for the listing of lapatinib (Tykerb) on the Pharmaceutical Schedule for the treatment of patients with trastuzumab-resistant metastatic HER-2 positive breast cancer, either as single agent therapy or in combination with chemotherapy as selected by the patient’s Medical Oncologist.

Recommendation

- 14.2 The Committee **recommended** that the application be declined.

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;(v)The cost-effectiveness of meeting health needs by funding*

pharmaceuticals rather than using other publicly funded health and disability support services;(vi)The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.

Discussion

- 14.3 The Committee noted that it had previously considered an application from the supplier, GlaxoSmithKline, for the funding of lapatinib in the same patient population at its meeting in November 2007. The Committee noted that at that time it recommended the application be declined.
- 14.4 The Committee reviewed evidence from a number of studies (published and unpublished), however, members noted that there was no new evidence presented, compared with that reviewed in 2007, that directly supported the use of lapatinib in the patient population requested for funding. Members noted that the main evidence in this patient population remained that from study EGF100151 (Geyer et al NEJM 2006) for which an updated report had now been published (Cameron et al Breast Cancer Res Treat 2008).
- 14.5 The Committee noted that in EGF100151 399 women with HER2-positive, locally advanced or metastatic breast cancer previously treated with anthracycline-, taxane-, and trastuzumab-containing regimen were randomised 1:1 to receive either combination lapatinib and capecitabine or monotherapy capecitabine. Members noted that the initial publication (Geyer et al 2006) reported a small but statistically significant benefit in median time to disease progression (TTP) for the lapatinib plus capecitabine arm, compared with the capecitabine monotherapy arm (8.4 months vs. 4.4 months), however, there was no difference in overall survival at that time. Members noted that the updated publication (Cameron et al 2008) reported a non significant 4% absolute difference in survival with a 22% reduction in hazards of death I (HR: 0.78, 95% CI: 0.55-1.12, P = 0.177).
- 14.6 The Committee considered that in the patient population requested for funding lapatinib offered a modest benefit in terms of delaying disease progression, without any survival advantage. Members noted that lapatinib was an expensive treatment given its modest benefits.
- 14.7 The Committee considered that it could not support the funding of lapatinib in the indication sought. However, members noted that lapatinib may have a place earlier in therapy, and would consider an application, with supporting evidence, for the funding of lapatinib as first line treatment in HER2-positive patients with metastatic breast cancer (in place of currently funded trastuzumab).

15 Nab-paclitaxel (Abraxane) for advanced breast cancer

Application

- 15.1 The Committee considered an application from Specialised Therapeutics Limited for the listing of nab-paclitaxel (Abraxane) on the Pharmaceutical Schedule for the treatment of

patients with advanced (metastatic) breast cancer after failure of prior therapy including an anthracycline.

Recommendation

- 15.2 The Committee **recommended** that nab-paclitaxel should be funded on the Pharmaceutical Schedule for the treatment of patients with advanced (metastatic) breast cancer after failure of prior therapy including an anthracycline only if cost neutral to weekly paclitaxel, taking into account pharmaceutical and other health sector costs and cost offsets.

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;* (v) *The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services;* (vi) *The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 15.3 The Committee noted that nab-paclitaxel was a nanoparticle albumin-bound formulation of the taxane paclitaxel. Members noted that standard paclitaxel had low aqueous solubility which necessitated formulation with polymethoxylated castor oil (Cremophore-EL) and ethanol. Members further noted that Cremophore-EL was associated with hypersensitivity reactions which necessitated corticosteroid and antihistamine premedication in patients receiving paclitaxel which had their own side effects.
- 15.4 The Committee considered that the nab-paclitaxel formulation addressed some of the toxicity issues of the standard paclitaxel formulation and there were biological arguments for increased cellular uptake and tissue localisation.
- 15.5 The Committee reviewed evidence from three randomised controlled studies in patients with metastatic breast cancer, two comparing nab-paclitaxel with paclitaxel (CA012 and CA021) and the third comparing nab-paclitaxel with docetaxel (CA024), another taxane. Members noted that both paclitaxel and docetaxel were funded on the Pharmaceutical Schedule for patients with metastatic breast cancer.
- 15.6 The Committee considered that overall the evidence demonstrated that nab-paclitaxel (260mg/m² administered over 30 minutes every three weeks) had similar efficacy to docetaxel (100 mg/m² administered every three weeks) or paclitaxel (175 mg/m² administered every three weeks). Members noted that nab-paclitaxel appeared superior in some sub-analyses, however, members considered that these results should be treated with caution due to the multiple number of analyses undertaken.
- 15.7 The Committee considered that the strength of the evidence provided was weak and the quality was moderate. In particular members considered that the comparator arm in the paclitaxel studies (paclitaxel 175mg/m² given intravenously over three hours every three weeks for 6 cycles) was suboptimal and did not reflect current clinical practice which was to administer paclitaxel weekly (80mg/m² intravenously over one hour every week).

Members considered weekly paclitaxel to be more efficacious compared with three weekly paclitaxel.

- 15.8 The Committee considered that nab-paclitaxel did offer some advantages over paclitaxel and docetaxel in terms of toxicity, with less risk of febrile neutropenia compared to docetaxel and less risk of peripheral neuropathy. Members considered nab-paclitaxel's main benefit to be lack of hypersensitivity risk and no requirement for premedication compared with paclitaxel. However, members noted that previous hypersensitivity to taxanes was a contraindication for nab-paclitaxel.
- 15.9 The Committee considered that, if funded for patients with metastatic breast cancer, nab-paclitaxel would replace paclitaxel in treatment algorithms, either as first or second line treatment depending on the treating oncologists' preference for first and second line taxanes in this population. Members noted that generic brands of both paclitaxel and docetaxel were now available, and that the price of these treatments had recently decreased significantly, with further price decreases expected in the future.
- 15.10 The Committee noted that while nab-paclitaxel was more expensive than paclitaxel, there may however be other cost offsets that would reduce its overall cost to the health sector, e.g. less hospital visits and reduced nursing resource and infusion time compared with weekly paclitaxel, and no requirement for premedication.
- 15.11 The Committee also noted that nab-paclitaxel has novel pharmacokinetic and tissue localisation properties, and considered that rare or unexpected toxicities might yet manifest following further market experience.

16 Fluticasone/salmeterol (Seretide) for asthma

Application

- 16.1 The Committee considered a two part Application from GlaxoSmithKline New Zealand Limited for the listing of high dose Seretide (250 µg fluticasone / 50 µg salmeterol metered dose inhaler (MDI) or Seretide accuhaler (500 µg fluticasone / 50 µg salmeterol) for the treatment of asthma and COPD under a Special Authority endorsed by a Specialist and the removal of the requirement for patients to be on individual inhaled corticosteroid (ICS) and long acting beta agonist (LABA) inhalers for three months prior to a prescription of the combination Seretide or Seretide Accuhaler.

Recommendation

- 16.2 The Committee **recommended** declining the application to list higher strength fluticasone/salmeterol (Seretide) inhalers on the Pharmaceutical Schedule.

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 in 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.

- 16.3 The Committee **recommended** the removal of the three month trial period from the Special Authority pertaining to prescriptions for combination inhaled corticosteroids with Long-acting Beta-Adrenoceptor Agents with a medium priority.

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; (v) The cost-effectiveness in meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

- 16.4 The Committee considered the prescribing and dispensing pattern of New Zealand compared to the United Kingdom, the Netherlands and Australia who have the high dose presentations subsidised (IMS data (MIDAS Retail and Hospital) for the 2009 calendar year as supplied by GSK). The use of individual ICS inhalers in New Zealand is comparable to that in the UK and higher than Australia. New Zealand has a lower use of combination inhalers than both the UK and Australia.
- 16.5 The Committee noted the Bateman et al paper (Am J Resp Crit Care Med 2004;170:836-844, the GOAL study). 3,421 patients were enrolled in this one year randomised controlled trial that studied the up-titration of fluticasone or fluticasone/salmeterol to achieve the Global Initiative for Asthma (GINA) 'total control' guideline. A high proportion of patients obtained 'total control' on a high dose combination inhaler. The high level of symptomatic control was at the expense of upper respiratory tract infections and nasopharyngitis (13-14%), oral thrush and hoarseness (~3% for both groups) and depressed cortisol/creatinine ratios (~8% in both groups). There was no step down protocol in this study.
- 16.6 The Committee noted a more recent study by Lundbeck et al (Respir Med 2009;103:348-355), which examined 282 randomised patients from a cohort of 4,000 patients with mild to moderate asthma previously treated with less than 1,200µg per day budesonide. Other inclusion/exclusion criteria were poorly described. Following a two month run-in period, during which they received a maximum dose of budesonide of 400µg/day or equivalent, patients were randomised into three groups to receive blinded treatment with salmeterol (SAL) 50 µg BD; fluticasone (FP) 250µg BD or salmeterol/fluticasone 50/250µg (FSC) via diskus inhaler for 12 months. Patients whose asthma was not controlled had an additional daily dose of FP 250µg BD and entered the open-label phase of the study. Patients who remained controlled continued with blinded treatment for 12 months before entering the two year open phase. At the end of year one, 61% of SAL, 35% of FP and 11% of FSC patients required an increase in treatment. Treatment was increased or decreased over the next two years dependent on the degree of control. By the end of the three years 73% of the subjects remaining in the study were receiving FSC compared

with 21% receiving FP and 5% on SAL. Of the 73% on FSC at the end of three years, 24% were on high dose (500 µg / 50 µg). Safety assessments showed the usual side effect profiles appearing in all three groups and mean serum cortisol levels were said to be in the normal range for all groups. Members noted that this study is useful due to its duration and the observation of a 'real life' response by clinicians to changes in asthma control. However, they noted that the methodology is weakened by being open label in the last two years and the small number of patients and small study team.

- 16.7 Members noted the TORCH study (Calverly et al NEJM 2007;356;8:775-789) for treatment of COPD. 6112 patients were enrolled in this randomised controlled trial comparing FSC at a dose of 500 µg / 50 µg with placebo alone, SAL alone or FP alone, over a period of three years. This study showed that FSC had a modest benefit in exacerbation rates and symptom scores over SAL alone but there was no benefit in terms of mortality, and the FSC group had a higher rate of pneumonia (19.6%) than in the FP and placebo groups (18.3% and 12.3% respectively).
- 16.8 The Committee noted the INSPIRE study which was a head to head study of Seretide vs. tiotropium in patients with severe COPD (FEV₁ <50% predicted with a mean of 39%). There was no improvement in exacerbation rate, a small benefit in symptoms and a slight benefit in terms of all causes of mortality. However, there was a difference in drop out rates – more from the tiotropium arm – raising the issue of a healthy survivor effect biasing the result. The study was underpowered with respect to differences in mortality. As in the TORCH study, the steroid-based treatment was associated with a higher incidence of pneumonia.
- 16.9 Members also noted the results of a Canadian trial (Aaron et al, Ann Intern Med.2007;146:545-556) comparing tiotropium with placebo, SAL or FSC. No improvement was seen in the rate of exacerbations requiring antibiotics or oral steroids, but there was some benefit of reduced hospitalisation rates for exacerbations in the tiotropium/FSC arm. More than 40% of patients receiving tiotropium plus placebo or tiotropium plus SAL did not complete the study.
- 16.10 Other studies noted were the Kardos study (Kardos et al, Am J Respir Crit Care Med 2007;175:144-149) and the Singh trial (Singh et al, Thorax 2008;63:592-598). The Kardos study was previously reviewed by PTAC in 2007 and was supportive of SFC 500 µg / 50 µg vs. SAL, but cases of suspected pneumonia were higher in the SFC group vs. the SAL group. The Singh trial showed improvement in lung function parameters and reduced SABA use for patients on tiotropium and fluticasone/salmeterol ("triple" therapy) vs. the individual components.
- 16.11 In summary, the Committee noted that there seems to be some evidence in supporting fluticasone/salmeterol in COPD, but when limiting the consideration to "high dose", 500µg / 50µg BD Seretide the evidence is less firm (INSPIRE and TORCH) with variable effects on mortality and exacerbation rates and remaining concerns regarding the increased incidence of pneumonia. The Committee considered that there seems to be no evidence of a dose-response effect when the inhaled steroid component of the fluticasone/salmeterol is increased, although a case-control study has suggested a dose response effect for pneumonia in the higher dose ICS.
- 16.12 The Committee noted that the strength and quality of the evidence supplied in the application for asthma was fair only and agreed that most patients with asthma can be

controlled on relatively small doses of ICS and all the guidelines suggest stepdown trials once control has been obtained. The Committee accepted that some patients with asthma require high dose combination therapies, but such combinations can be made up of the existing subsidised inhalers.

- 16.13 The Committee noted that for COPD, the fixed dose combination (FDC) inhalers have been shown to improve health status, decrease exacerbations and improve lung function. Combination therapy increases the likelihood of pneumonia, and the largest prospective trial failed to demonstrate an improvement in mortality. ICS and FDC inhalers have the side effects of oral candidiasis (NNH = 38) and hoarseness (NNH = 35) such that most COPD guidelines would suggest using ICSs only in severe COPD with frequent exacerbations, with the earlier use of anticholinergics or short or long acting beta-agonists.
- 16.14 Members considered that the listing of a high dose FDC inhaler would lead to an increase in prescribing of high dose corticosteroids, as inevitably there would be dose creep.
- 16.15 The Committee noted that in February 2010, the FDA issued a Press Release stating that LABAs should not be used in asthma without an asthma controller medication. This followed two studies – the SMART trial (Nelson et al. Chest 2006;129:15-26) and the SNS (Castle et al BMJ 1993;306:1034-7) and a meta-analysis conducted by the FDA in 2008. The results of these studies indicated an increased risk of severe exacerbation (asthma related death, intubation or hospitalisation) for those patients using LABAs alone, with the largest risk being those in the 4-11 year age group (risk difference 14.8 per 1,000). The FDA was unable to determine whether the addition of an ICS to a LABA reduces or eliminates that risk, but the FDA warning includes the advice that paediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid should use a combination product.
- 16.16 The Committee noted that Professor Richard Beasley's group (Weatherall et al, Thorax 2010;65:39-43) had conducted a meta-analysis of 215 studies in the GSK database. Members noted that one of the main findings from this meta-analysis is that the use of salmeterol alone in unstable asthma increases the risk of death and that the risk is reduced with concomitant ICS therapy. In 63 studies the fixed dose combination inhaler was compared to ICS therapy and there were no deaths from asthma observed, therefore there was no evidence of increased mortality risk with the FDC product, but with the important proviso that this interpretation is limited by the low statistical power of the available studies to detect this endpoint.
- 16.17 The Committee noted that Professor Beasley's group (Beasley et al, Lancet 2010; 376:750-1) had also called for the withdrawal of LABA monotherapy use in asthma, and that the British Asthma Guidelines stress the importance of taking a LABA with an inhaled corticosteroid.
- 16.18 The Committee noted that it had last considered the issue of combination inhalers in 2007, and that since then there have been significant developments in quantifying the risks with using sole LABA devices alone in asthma, particularly in younger patients. The Committee noted issues with non-compliance and sub-optimal ICS use. Consequently, members noted that it is becoming increasingly harder to justify a period of separate

LABA and ICS prescriptions to asthma patients who, by guideline recommendations, merit combination LABA and ICS treatment.

17 Rivastigmine patches (Exelon) for Alzheimer's disease

Application

- 17.1 The Committee considered an Application from Novartis New Zealand Limited for the listing of rivastigmine patches (Exelon) on the Pharmaceutical Schedule for the treatment of Alzheimer's disease in patients intolerant to donepezil tablets.

Recommendation

- 17.2 The Committee **recommended** that rivastigmine patches be listed on the Pharmaceutical Schedule subject to the following Special Authority criteria with a low priority:

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

Both:

- 1 The patient has been diagnosed with dementia; and
- 2 The patient has experienced intolerable nausea and/or vomiting from donepezil tablets.

Renewal from any relevant practitioner. Applications valid for 12 months for applications meeting the following criteria:

Both:

- 1 The treatment remains appropriate; and
- 2 The patient has demonstrated a significant and sustained benefit from treatment.

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;* (vi) *The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule,* (vii) *The direct cost to health service users.*

Discussion

- 17.3 The Committee noted that it had previously considered rivastigmine tablets, both as an individual funding application and in the context of a review of acetylcholinesterase inhibitors as a group (donepezil, rivastigmine and galantamine). The Committee reiterated its previous view that the three acetylcholinesterase inhibitors provide broadly similar efficacy.
- 17.4 The Committee considered that approximately 20% of patients are unable to tolerate the gastrointestinal side effects of donepezil tablets (which were funded on 1 November 2010) and that this generally leads to treatment discontinuation. The Committee noted that patients who are unable to tolerate therapeutic doses of donepezil tablets are unlikely to be able to tolerate any acetylcholinesterase inhibitor taken orally. The

Committee considered that there was an unmet clinical need for a different presentation of an acetylcholinesterase inhibitor in these patients.

- 17.5 The Committee noted that the supplier had originally requested funding of rivastigmine patches as a first-line treatment for dementia but had amended its Application to include a request for second-line funding following PHARMAC's decision to fund donepezil tablets.
- 17.6 The Committee considered that there was good evidence to show that rivastigmine patches (one 10 cm² patch per day) provide similar efficacy to rivastigmine capsules (12 mg per day), with reduced gastrointestinal side effects (Winblad et al. *Neurology* 2007;69(4 Suppl 1):S14-S22). The Committee noted, however, that skin reactions from patches are common and may result in discontinuation of treatment.
- 17.7 The Committee noted that the Mental Health Subcommittee had reviewed the Application in June 2010 and had recommended that rivastigmine patches be funded, subject to Special Authority criteria restricting their use to patients who cannot tolerate donepezil tablets, with a medium priority. The Committee broadly agreed with the views of the Mental Health Subcommittee in relation to rivastigmine patches.
- 17.8 However, the Committee noted its concerns around the large difference in pricing between donepezil tablets and rivastigmine patches and the high estimated budget impact. The Committee noted that at the proposed pricing rivastigmine patches would not be particularly cost effective and considered that there was a high financial risk that, if funded, the patches could be used long-term in patients who were not receiving benefit. In addition, the Committee considered that it would be important to limit access to rivastigmine patches to patients with true intolerance to donepezil tablets, to reduce the financial risk from rivastigmine patches being used because of patient or caregiver preference for patches over tablets.

18 Adalimumab (Humira) for juvenile idiopathic arthritis

Application

- 18.1 The Committee considered an Application from Abbott Laboratories NZ Limited to widen access to funded adalimumab to include treatment of juvenile idiopathic arthritis (JIA) subject to the same Special Authority criteria as etanercept.

Recommendation

- 18.2 The Committee **recommended** that access to adalimumab be widened in the Pharmaceutical Schedule to include treatment of JIA, subject to similar Special Authority criteria to those applying to etanercept in this indication but with a note encouraging the use of adalimumab in combination with methotrexate, only if it was cost-neutral to the Pharmaceutical Budget.

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;* (v) *The cost-effectiveness of meeting health needs by*

funding pharmaceuticals rather than using other publicly funded health and disability support services, (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.

Discussion

- 18.3 The Committee noted that adalimumab is currently funded, subject to Special Authority criteria, as a last-line treatment for rheumatoid arthritis, chronic plaque psoriasis, psoriatic arthritis, ankylosing spondylitis and Crohn's disease.
- 18.4 The Committee noted that currently there were two funded last-line tumour necrosis factor (TNF) alpha inhibitor treatments for adults with rheumatoid arthritis (adalimumab and etanercept) but only one funded last-line TNF-alpha inhibitor treatment for patients with JIA (etanercept).
- 18.5 The Committee noted that clinical trial evidence (Lovell et al. N Engl J Med 2000;342:763-9) suggests that approximately 25% of patients with JIA do not receive optimal benefit from treatment with their first TNF-alpha inhibitor and, as such, the Committee considered that there is an outstanding need for a second biologic treatment in this patient group.
- 18.6 The Committee noted that the key evidence for adalimumab in JIA came from DE038, a placebo-controlled randomised clinical trial of adalimumab in patients aged 4 to 17 years with JIA who had previously received treatment with non-steroidal anti-inflammatory drugs (NSAIDs) (Lovell et al, N Eng J Med 2008;359:810-820). Exclusion criteria included ongoing or serious infection and having ever been treated with a biologic agent. Use of methotrexate and corticosteroids was permitted. Response was assessed using measures of disease improvement (using the Paediatric American College of Rheumatology (PedACR) measure) or disease flare. Patients were administered adalimumab (24 mg per m² body surface area, to a maximum of 40 mg) fortnightly for 16 weeks. One hundred and forty four patients (80 of 85 who were taking concomitant methotrexate and 64 of 86 patients who were not) had a PedACR 30 response at 16 weeks. One hundred and thirty three of these patients (75 who were taking concomitant methotrexate and 58 who were not) were then randomly assigned to receive adalimumab or placebo for up to 32 weeks. The primary endpoint was the proportion of patients with disease flare during the 32-week double-blind phase. Among patients receiving methotrexate, flares occurred in 37% of adalimumab patients and 65% of placebo patients (p=0.02). Among patients not receiving methotrexate, flares occurred in 43% of adalimumab patients and 71% of placebo patients (p=0.03). At the end of the study (48 weeks) PedACR 30, 50 and 70 responses were seen in significantly more adalimumab patients than in placebo patients for those on concomitant methotrexate but there was no statistically significant difference between the adalimumab and placebo groups in patients not receiving methotrexate.
- 18.7 The Committee considered that DE038 provided good quality evidence of efficacy of adalimumab in JIA, although the Committee considered that the results may not be directly applicable to the New Zealand setting given that the inclusion criteria differed from the proposed Special Authority criteria. In addition, only those patients who responded to adalimumab in the open-label phase were included in the double-blind phase of the trial, which is not directly comparable to clinical practice.

- 18.8 The Committee noted that there were no trials directly comparing adalimumab with etanercept in JIA and that the supplier had provided an indirect comparison analysis using results from the key adalimumab and etanercept trials (Lovell et al. N Engl J Med 2000;342:763-9; Lovell et al, N Eng J Med 2008;359:810-820), which had a similar design, using the placebo arms of the trials as a common reference. The Committee noted the supplier's claim that the analysis demonstrates that adalimumab is non-inferior to etanercept. However, the Committee considered that, taking into account the lack of a trial directly comparing these treatments, the considerable differences between the two studies in terms of baseline characteristics and duration of the open-label and double-blind phases and the differences between the placebo and etanercept groups at randomisation, the supplier's analysis should be interpreted with caution. However, on balance, the Committee considered that the trial results suggested that the efficacy of both agents in JIA was broadly similar and the side effect profiles were broadly comparable although it appeared that adalimumab may be associated with fewer adverse effects.
- 18.9 The Committee noted that the dosing schedule for adalimumab (one injection per fortnight) was more favourable than etanercept (one or two injections per week) and that patients would prefer fewer injections.
- 18.10 The Committee noted that the supplier had not provided evidence of efficacy of adalimumab in patients who had received suboptimal benefit from etanercept, although it was reasonable to assume that adalimumab would have the potential for some benefit in such patients (as is seen in other indications).
- 18.11 The Committee considered that on the basis of the available evidence there would be no justification for the price of adalimumab to be higher than that of etanercept, nor would there be any reason for different access criteria to apply. However, the Committee noted that the Special Authority criteria for etanercept were now several years old and it might be worthwhile conducting a review of the criteria to ensure they reflect current practice.
- 18.12 The Committee considered that the estimates of patient numbers by PHARMAC staff if adalimumab was funded were potentially on the low side, given that clinicians are experienced with using adalimumab, and agreed with the assumption that the majority of patients (at least 85%–90%) would be on 40 mg per fortnight, based on the age and weight distribution of the current etanercept patients.
- 18.13 The Committee noted that the results of DE038 suggest that adalimumab is considerably more effective when taken with methotrexate in patients with JIA and that this should be encouraged if adalimumab was funded.

19 Paracetamol with ibuprofen (Maxigesic) for analgesia

Application

- 19.1 The Committee considered an Application from AFT Pharmaceuticals for the listing of paracetamol 500 mg with ibuprofen 150 mg tablets (Maxigesic) on the Pharmaceutical Schedule for the relief of pain and reduction of fever and inflammation.

Recommendation

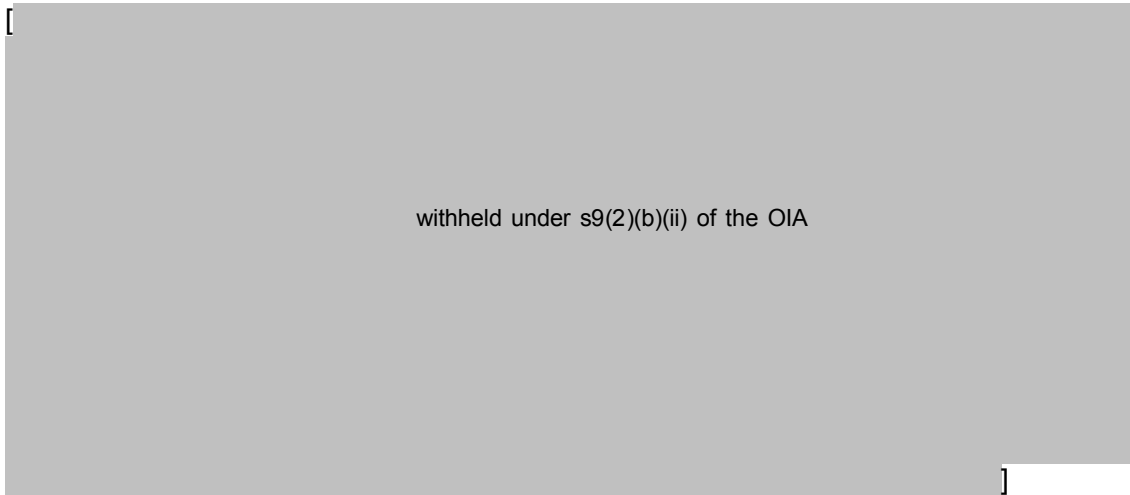
- 19.2 The Committee **recommended** that the Application for paracetamol 500 mg with ibuprofen 150 mg (Maxigesic) on the Pharmaceutical Schedule for the relief of pain and reduction of fever and inflammation be declined because of lack of evidence of efficacy, safety or improved compliance when compared with the individual components taken together.

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; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule, (vii) The direct cost to health service users.*

Discussion

- 19.3 The Committee reviewed two studies provided by the supplier in support of the Application. The first (MX-1) was a double-blind randomised controlled trial in which 135 adults undergoing wisdom tooth extraction were randomised to receive paracetamol 500 mg with ibuprofen 150 mg, paracetamol 500 mg alone or ibuprofen 150 mg alone (Merry et al. Br J Anaesth 2010;104-80-88). Subjects were instructed to take two tablets before the operation then two tablets every six hours for up to 48 hours. Participants rated their pain on a 100 mm visual analogue scale (VAS) before and immediately after the operation, then every 1–2 hours while awake for 48 hours. The primary outcome measure was the area under the curve (AUC) of the VAS rating divided by time, at rest and on activity (jaw opening). Secondary outcomes were global pain rating and global nausea rating at the end of the study period, number of episodes of vomiting over the study period, rating of sleep disturbance on a 100 mm VAS and rescue analgesia consumption. There was a statistically significant difference between paracetamol 500 mg with ibuprofen 150 mg and either paracetamol 500 mg alone or ibuprofen 150 mg alone for the primary outcome measure and in the global pain rating, in favour of the combination product. There was no significant difference between the combination product and the individual components taken alone for any of the other secondary endpoints. The adverse event reports suggested that the combination product has no additional risk of adverse events compared with paracetamol 500 mg or ibuprofen 150 mg alone, although the patient numbers were too small to make meaningful comparisons between groups.
- 19.4 The Committee considered that the MX-1 study had a number of limitations, in particular that it was conducted in a small number of patients and there was no comparison between the combination product and its individual components taken together or the standard dose of ibuprofen used in New Zealand (200–400 mg every four to six hours). The Committee noted that the study has been criticised on a number of points (Knox GM, Letter to Br J Anaesth 5 February 2010), which have been rebutted by the study authors (Merry et al, Letter to Br J Anaesth 15 February 2010). The Committee agreed with the concerns of Knox regarding the method of statistical analysis used (use of a one-tailed, rather than two-tailed, sample size estimate) and also felt that a 9 mm reduction on a 100 mm VAS was of questionable clinical significance. Further, the Committee noted that there was no significant difference between the groups in use of rescue medication, which was used in more than half of all study participants. In addition, no other dosing schedules were investigated and, as such, the optimal dose of the combination product is unknown.

19.5



withheld under s9(2)(b)(ii) of the OIA

- 19.6 Overall, the Committee considered that the quality and strength of the evidence was weak, with limited evidence of efficacy and safety of the combination versus paracetamol alone or ibuprofen alone.
- 19.7 The Committee considered that the only true comparator for a combination product is its separate components taken together and there was no evidence provided to support the efficacy, safety or improved compliance of paracetamol 500 mg with ibuprofen 150 mg compared to the individual components prescribed together (whether taken separately or at the same time).
- 19.8 The Committee considered that there was no reason why paracetamol 500 mg and ibuprofen 200 mg (the lowest funded dose in New Zealand) couldn't be taken at the same time, taking into account the recommended dosing schedules on the Medsafe datasheet. The Committee considered that this could provide similar, or possibly greater, efficacy than the combination product, given that the optimum dose of ibuprofen plus paracetamol is unknown.
- 19.9 The Committee considered that if it was funded paracetamol 500 mg with ibuprofen 150 mg would be used instead of paracetamol 500 mg and ibuprofen 200 mg and, to a lesser extent, other non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol 500 mg with codeine 8 mg, codeine 15 mg and 30 mg and tramadol 50 mg. The Committee considered that there were currently no problems with access to alternative treatments and that a paracetamol with ibuprofen combination product would not fill any unmet clinical need.
- 19.10 The Committee considered that the high price of paracetamol 500 mg with ibuprofen 150 mg relative to the price of paracetamol 500 mg plus the price of ibuprofen 200 mg would likely outweigh any savings from reductions in dispensing fees in patients receiving both paracetamol and ibuprofen (assuming all presentations are dispensed stat and are prescribed for a month or more), although the cost to the patient would be lower as there would be fewer co-payments.

20 Modafinil (Modavigil) for narcolepsy

Application

20.1 The Committee reconsidered an Application from CSL Biotherapies for the listing of modafinil (Modavigil) on the Pharmaceutical Schedule for the treatment of narcolepsy.

Recommendation

20.2 The Committee **recommended** that modafinil be listed on the Pharmaceutical Schedule as a second-line treatment for hypersomnia associated with narcolepsy subject to the following Special Authority criteria with a medium priority:

Initial application only from a neurologist or respiratory specialist. Approvals valid for 24 months for applications meeting the following criteria:

All of the following:

- 1 The patient has a diagnosis of narcolepsy and has excessive daytime sleepiness associated with narcolepsy occurring almost daily for three months or more; and
- 2 Either:
 - 2.1 The patient has a multiple sleep latency test (MSLT) with a mean sleep latency of less than or equal to 8 minutes and 2 or more sleep onset rapid eye movement periods; or
 - 2.2 The patient has at least one of: cataplexy, sleep paralysis or hypnagogic hallucinations; and
- 3 Either:
 - 3.1 An effective dose of a subsidised formulation of methylphenidate or dexamphetamine has been trialled and discontinued because of intolerable side effects; or
 - 3.2 Methylphenidate and dexamphetamine are contraindicated.

Renewal application only from a neurologist or respiratory specialist. Approvals valid for 24 months where the treatment remains appropriate and the patient is benefiting from treatment.

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.*

20.3 The Committee **recommended** that modafinil be listed on the Pharmaceutical Schedule as a first-line treatment for hypersomnia associated with narcolepsy, subject to the same Special Authority criteria as for second-line but without criterion 3, only if it was cost-neutral versus dexamphetamine and methylphenidate hydrochloride (immediate-release and sustained-release tablets).

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.*

Discussion

- 20.4 The Committee noted that it had previously considered the application for modafinil in February 2007 and had recommended that it be funded subject to the following Special Authority criteria for patients with diagnosed excessive daytime sleepiness associated with narcolepsy who could not tolerate methylphenidate and dexamphetamine or in whom methylphenidate and dexamphetamine were contraindicated, with a low priority:

Initial application only from a neurologist or respiratory specialist. Approvals valid for 24 months for applications meeting the following criteria:

All of the following:

- 1 The patient has excessive daytime sleepiness associated with narcolepsy occurring almost daily for three months or more; and
- 2 Hypersomnia not better explained by another disorder; and
- 3 Either:
 - 3.1 Definite history of cataplexy and a Multiple Sleep Latency Test (MSLT) with a mean sleep latency less than or equal to 8 minutes; or
 - 3.2 A MSLT with a mean sleep latency of less than or equal to 8 minutes and 2 or more sleep onset rapid eye movement periods; and
- 4 The MSLT must be preceded by nocturnal polysomnography and sleep prior to the MSLT must be at least 6 hours; and
- 5 Either:
 - 5.1 An effective dose of a subsidised formulation of methylphenidate or dexamphetamine has been trialled and discontinued because of intolerable side effects; or
 - 5.2 Methylphenidate and dexamphetamine are contraindicated.

Renewal application only from a neurologist or respiratory specialist. Approvals valid for 24 months where the treatment remains appropriate and the patient is benefiting from treatment.

- 20.5 The Committee noted that in July 2010 PHARMAC consulted on a proposal to fund modafinil as a second-line treatment for hypersomnia associated with narcolepsy subject to Special Authority criteria essentially similar to those recommended by PTAC in February 2007, but that this proposal was now on hold pending updated advice from PTAC. The Committee noted that PHARMAC staff were seeking PTAC's advice in relation to issues raised during consultation (in particular around requests for modafinil to be available as a first-line treatment for narcolepsy and for the removal of the requirement for MSLTs to be performed because these tests are not consistently funded or available across New Zealand), published literature identified by consultation responders, and a cost-utility analysis performed by PHARMAC staff. The Committee noted that the supplier had not submitted additional information for review.
- 20.6 The Committee considered that the publications provided did not contain any new clinical trial evidence of relevance to the modafinil application. The Committee reiterated its view that the randomised placebo-controlled studies it had reviewed in 2007 were of good strength and quality and showed that modafinil was associated with significant improvements in primary and secondary outcome measures in patients with excessive daytime sleepiness associated with narcolepsy.
- 20.7 Although the Committee considered that the available evidence suggested that modafinil would be effective as a first-line treatment for narcolepsy, it was noted that there did not appear to be any clinical trials specifically investigating modafinil as a first-line agent and

that approximately 70% of people in the clinical trials had received previous medical treatment for narcolepsy.

- 20.8 The Committee considered that there was currently no clinical trial evidence to suggest that modafinil provides superior efficacy to the stimulants currently funded for first-line use in narcolepsy (dexamphetamine and methylphenidate). The Committee noted that the side effect profile of modafinil differs to that of the stimulants but that it was not without side effects, in particular anxiety and nervousness had emerged as the main reason for discontinuation due to side effects in the extension studies of the randomised controlled trials. The Committee considered that modafinil appeared to have reduced potential for tolerance to its therapeutic effects than the stimulants. The Committee reiterated its previous view that there is significant potential for abuse and diversion of modafinil, although members considered that this would be for different reasons than those relating to the abuse and diversion of the stimulants.
- 20.9 Overall, the Committee considered that there was no good evidence to suggest that modafinil would be associated with any significant health gains if it was used instead of dexamphetamine or methylphenidate as a first-line treatment, with the exception of patients who might experience intolerable side effects from the stimulants (estimated to be approximately 10% of patients). The Committee agreed with inputs and assumptions by PHARMAC staff in the CUA for modafinil as a first-line treatment for narcolepsy, noting that the result of approximately \$380,000 per quality adjusted life year (QALY) was largely driven by the high cost of modafinil versus the stimulants.
- 20.10 The Committee considered that there was insufficient evidence to support the claim from consultation responders that the efficacy of modafinil is reduced in patients who have previously been treated with methylphenidate or dexamphetamine.
- 20.11 The Committee considered that there is a lack of alternative treatments for narcolepsy in patients who are intolerant to stimulants or in whom stimulants are contraindicated. The Committee noted that antidepressants and selegiline are sometimes used in this patient group; however, this would be an off-label use of these agents and there is limited evidence of their efficacy.
- 20.12 The Committee largely agreed with inputs and assumptions by PHARMAC staff in the CUA for modafinil as a second-line treatment for narcolepsy. The Committee considered that the assumed QALY gain was reasonable, although Members considered that it may slightly favour modafinil. The Committee considered the potential for misuse of modafinil was likely to be greater than estimated in the model and recommended this be amended in the analysis.
- 20.13 The Committee noted that both Medsafe and international regulators are currently reviewing the registered indications for modafinil with a view to restricting the indication to narcolepsy because of the unfavourable risk:benefit profile in other indications.
- 20.14 The Committee considered that if modafinil was funded it should be subject to Special Authority criteria because of cost and to ensure that it was funded only for patients with narcolepsy.
- 20.15 The Committee considered that a requirement for MSLT in the Special Authority would be reasonable; however, members accepted that consultation responders had identified

access to these tests as an issue. The Committee considered that if an MSLT was not able to be performed there should be a requirement for patients to have at least one of cataplexy, sleep paralysis or hypnagogic hallucinations – in line with the inclusion criteria for the clinical trials and with the clinical diagnostic criteria for narcolepsy.

- 20.16 The Committee considered that, in theory, funding modafinil for narcolepsy should not grow the overall funded market for narcolepsy treatments if the access criteria were strictly adhered to. However, the Committee considered that the number of patients with current Special Authority approvals for methylphenidate or dexamphetamine for narcolepsy (around 200) appeared high. The Committee considered that this was an issue which should be reviewed by the Neurological Subcommittee.