

PTAC meeting held 21 & 22 February 2008 (minutes for web publishing)

PTAC minutes are published in accordance with the following definitions from the PTAC Guidelines 2002:

“**Minute**” means that part of the record of a PTAC or Sub-committee meeting (including meetings by teleconference and recommendations made by other means of communication) that contains a recommendation to accept or decline an application for a new investment or a clinical proposal to widen access and related discussion.”

Note that this is not necessarily a complete record of the PTAC meeting; records relating to PTAC discussions about an application that do not contain a recommendation to accept or decline an application have not been published and some material has been withheld in accordance with the following withholding grounds in the Official Information Act 1982 (OIA) to:

- protect the privacy of natural persons (section 9(2)(a));
- protect information where the making available of the information would be likely to unreasonably prejudice the commercial position of the person who supplied or who is the subject of the information (section 9(2)(b)(ii));
- enable PHARMAC to carry on, without prejudice or disadvantage, negotiations, including commercial negotiations (section 9(2)(j)).

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Record of PTAC meeting held 8 & 9 November 2007

The Committee reviewed the record of the PTAC meeting held on 8 & 9 November 2007 and made the following minor amendments:

Lapatinib ditosylate (Tykerb) – paragraph 20.11: replace “The Committed” with “The Committee”.

Cabergoline Special Authority – paragraph 21.6: replace “and the patients would” with “and that patients would”.

Cabergoline Special Authority – paragraph 21.6: replace “determine any possible adverse cardiotoxicity” with “determine any possible cardiotoxicity”.

Review of Special Authority Criteria for Octreotide - paragraph 22.7: replace “EC applications had been approved, that widening of access to octreotide” with “EC applications had been approved, widening of access to octreotide”.

Sorafenib (Nexavar) for renal cell carcinoma

The Committee considered an application from Bayer New Zealand Ltd regarding the listing of sorafenib tosylate (Nexavar) on the Pharmaceutical Schedule for the treatment of patients with advanced (stage IV) renal cell carcinoma (RCC).

The Committee considered that there was a high unmet clinical need for better treatments for advanced renal cell cancer and that the only current treatment option, interferon, had limited efficacy and significant toxicity.

The Committee noted that sorafenib is an oral multiple kinase inhibitor of tumour cell proliferation and angiogenesis. The Committee further noted that it had reviewed an application for another multiple kinase inhibitor in renal cell cancer, namely sunitinib, at its February 2007 meeting. Members had expressed concerns about the high cost of sunitinib in the absence of a clinically meaningful survival improvement and referred the application to the Cancer Treatments Subcommittee (CaTSoP) for advice. Members noted that at CaTSoP’s December 2007 meeting, the Subcommittee considered that the very high cost of sunitinib was not justified for an essentially a palliative treatment with no demonstrated improvement in overall survival; therefore, CaTSoP recommended that the application be declined.

The Committee reviewed data provided in support of the application from two studies, a phase III study (TARGET, trial 11213, Escudier et al, NEJM 2007; 356:125-134) and a phase II study (trial 10039). Members noted that these studies compared sorafenib treatment with placebo; members also noted that the supplier provided data from various sunitinib studies, which included comparisons with interferon treatment, but there were no studies comparing sorafenib with interferon or sunitinib.

The Committee noted that in the TARGET study, patients were randomised to receive sorafenib (400mg twice daily) (n=451) or placebo (n=452); treatment (2 x 200mg tablets twice daily) was continued until a withdrawal criterion was reached (unacceptable toxicity, disease progression or death). A planned analysis of progression free survival was conducted in January 2005 and showed statistically significant benefit of sorafenib over placebo with progression free survival of 5.5 months in the sorafenib group compared with 2.8 months in the placebo group (Hazard Ratio (HR) 0.44, 95% CI 0.35-0.55, $p < 0.01$). Members noted that following release of these data the study was unblinded and amended to permit crossover from placebo to sorafenib from May 2005. A survival analysis performed on data from the May 2005 cut-off, that is prior to crossover, demonstrated that fewer patients had died on sorafenib (97 of 451, 22%) compared with placebo (123 of 452, 27%, HR 0.72, 95% CI 0.54-0.94, $p = 0.02$); however, members noted that the absolute difference (5%) was small.

The Committee considered that the crossover of patients from placebo to sorafenib in May 2005 made it impossible to evaluate longer-term data from this study meaningfully.

The Committee noted that in the TARGET study 13% of patients in the sorafenib group had dose reductions compared with 6% in the placebo group ($p < 0.001$); members noted that dose interruptions were most commonly due to dermatological adverse events (mainly hand foot syndrome) and gastrointestinal adverse events (mainly diarrhoea). Members also noted that hypertension was more frequent in the sorafenib group and that cardiac ischaemia or infarction occurred in 12 patients. Serious adverse events leading to hospitalisation or death were reported in 154 (34%) of patients in the sorafenib group compared with 110 (24%) in the placebo group. This included 46 (10%) deaths for sorafenib patients compared with 25 (6%) placebo patients ($p < 0.01$).

Members also reviewed an overall survival analysis of the TARGET study from September 2006 and noted that the estimated hazard ratio (risk of death with sorafenib compared with placebo) was 0.88 which was not statistically significant (95% CI 0.74 – 1.04). Overall survival at six months was 87.2% for the sorafenib group compared with 80% for the placebo group. Overall survival at 12 months was 65.1% (sorafenib) versus 58% (placebo).

The Committee considered that the data demonstrated that sorafenib was essentially a palliative treatment with modest disease stabilising activity; members noted that in the TARGET study only one patient had a complete response, 10% had a partial response and the remaining responders had stable disease. Members also considered that sorafenib had significant toxicity issues with a significant increase in deaths and hospitalisations due to adverse events.

The Committee noted that the Scottish Medicines Consortium (SMC) did not recommend sorafenib for funding in the NHS in Scotland, with the primary reasons being lack of data on overall survival and that cost effectiveness had not been demonstrated at £35,000/QALY (NZ\$98,000). Members also noted that in Australia the Pharmaceutical Benefits Advisory Committee (PBAC) had recommended against listing sorafenib, citing uncertain cost-effectiveness (likely cost per QALY greater than AU\$150,000) and uncertainty regarding extent of overall survival gain.

The Committee noted that the supplier had estimated that patients would be treated for six months; however, members considered that patients who responded to treatment or maintained stable disease are likely to be treated for longer, thus increasing costs.

The Committee considered that the cost of sorafenib was excessive for what is essentially a palliative treatment with significant toxicity; therefore, the Committee **recommended** that the application be declined.

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

Vinorelbine (Oral Navelbine) for non-small cell lung cancer

The Committee considered an application from Pierre Fabre Medicament Australia Pty Limited regarding listing of vinorelbine soft capsule (Navelbine Oral) on the Pharmaceutical Schedule for use as a single agent or in combination for the treatment of patients with non-small cell lung cancer (NSCLC).

The Committee noted that intravenous vinorelbine, as a single agent or in combination with other chemotherapy agents, is a treatment used in patients with advanced NSCLC. Members noted that in this setting treatment is purely palliative, with median survival of approximately 9 -10 months depending on the study examined.

The Committee noted that oral vinorelbine has a half-life of 38 hours. Members noted that bioequivalence studies have shown that oral vinorelbine administered at 60 mg/m² and 80 mg/m² are equivalent to 25 mg/m² and 30 mg/m² of IV vinorelbine respectively. Members also noted that oral vinorelbine is administered weekly for three doses, though the duration of each cycle of chemotherapy and the doses used are limited by adverse reactions.

The Committee reviewed data from a number of Phase II studies including a study (study CA 205, Jassem et al *Annals of Oncology* 2001;12(10);1375-81) comparing oral vinorelbine with intravenous vinorelbine in previously untreated patients with advanced NSCLC and studies examining the use of oral vinorelbine in combination with other chemotherapy agents. Members considered that the data demonstrated that oral vinorelbine was comparable to intravenous vinorelbine. Members noted that oral vinorelbine was associated with specific gastrointestinal side effects that did not occur with the intravenous form, including vomiting and diarrhoea.

The Committee considered that an oral formulation may have some advantages over an IV formulation, but noted that intravenous administration of vinorelbine only takes 6-10 minutes and might be used in combination with some other intravenous chemotherapy,

such as cisplatin. An oral formulation, therefore, would only have a minor advantage unless the oral form was being used as monotherapy.

The Committee considered that the supplier's estimate for the cost of intravenous administration of vinorelbine was too high and that its estimated patient numbers were extremely low. Members considered that the availability of an oral form of vinorelbine would grow the market, especially if that oral form was given as a single agent instead of intravenous vinorelbine plus some other intravenous chemotherapy, such as cisplatin. In summary, members considered that more patients would be treated with single agent oral vinorelbine, if it were funded, than are currently receiving intravenous vinorelbine.

The Committee noted that the supplier considered that oral vinorelbine would also replace some paclitaxel and gemcitabine usage and members considered that further advice from the Cancer Treatments Subcommittee of PTAC would be required to clarify whether this would be the case.

The Committee **recommended** that oral vinorelbine be listed in the Pharmaceutical Schedule for the treatment of NSCLC but only if cost neutral to the health sector. Members considered that assessment of cost should include potential growth in the vinorelbine market and costs relating to the management of the gastrointestinal side effects of the treatment requiring e.g. 5HT3 antagonists. Members also considered that cost offsets, such as reduced intravenous service costs associated with vinorelbine and other chemotherapy agent administration should be considered.

The Committee further **recommended** that the application be reviewed by the Cancer Treatments Subcommittee of PTAC for specific advice on the potential number of patients that would be treated, if oral vinorelbine would be used as monotherapy or combination treatment in these patients and the appropriate comparator treatments in these patients.

The Decision Criteria 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.*

Mycophenolate sodium (Myfortic) for prophylaxis of acute transplant rejection

The Committee considered an application from Novartis New Zealand for mycophenolate sodium (Myfortic) tablets to be listed on the Pharmaceutical Schedule under the same Special Authority criteria as currently apply to mycophenolate mofetil (Cellcept, Roche Products New Zealand Ltd).

Members noted that mycophenolate sodium (MPS) is an enteric coated sodium salt of the active metabolite mycophenolic acid (MPA), whereas the currently funded

mycophenolate mofetil (MMF) is the 2-morpholinoethyl (mofetil) ester of MPA. Members noted that MPS tablets are enteric coated which should theoretically reduce the incidence of gastrointestinal (GI) side effects. The Committee also noted that since MPS did not have the added molecular weight of the mofetil ester, a 720 mg dose of MPS contains the same amount of active MPA as 1000 mg of MMF, resulting in a smaller tablet size of MPS compared with MMF.

The Committee reviewed data from several bioequivalence, efficacy and safety studies comparing MPS with MMF. Members concluded that data from these studies demonstrated that MPS and MMF were therapeutically equivalent and have comparable safety and tolerability in both *de novo* and maintenance renal transplant patients and that it appears to be safe to switch patients from MMF to MPS.

[withheld under sections 9(2)(b)(ii) and 9(2)(j) of the OIA] members considered that it would be difficult to predict both how many existing transplant patients would be switched from MMF to MPS and how many new transplant patients would be initiated on MPS, rather than MMF. The Committee also noted that MPS is approved by Medsafe only for the prophylaxis of acute renal transplant rejections in adult patients receiving allogeneic renal transplants; however, the supplier had requested funding under the same Special Authority criteria as MMF, namely for acute organ rejection in patients receiving allogeneic renal or cardiac transplants or for transplant patients have severe tophaceous gout making azathioprine unsuitable.

Members considered that it would be important to maintain an oral liquid formulation of MPA for paediatric patients, and noted that whilst there was an oral liquid formulation of MMF there did not appear to be one for MPS.

The Committee **recommended** that mycophenolate sodium tablets be listed in the Pharmaceutical Schedule for the prophylaxis of acute renal transplant rejection in adult patients and gave this recommendation a medium to high priority.

The Decision Criteria 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.*

The Committee also considered an e-mail from [withheld under section 9(2)(a) of the OIA], requesting that access to MMF be extended to include treatment of liver transplant patients. Members considered that they require a full literature review and supporting data for use of MMF in these patients before making a recommendation for widening access on the Pharmaceutical Schedule. Members also considered that prior to the Committee making a recommendation in this patient population, advice from the Transplant and Immunosuppressants Subcommittee of PTAC should be obtained regarding use of mycophenolate for this indication.

The Committee also noted that there was currently a wide variety of applications through Exceptional Circumstances for off-label use of MMF, including use in liver, bone marrow

and lung transplantation as well as non-transplant indications such as treatment of lupus nephritis in patients failing azathioprine treatment.

Memantine for the treatment of severe behavioural disturbance in patients with moderate-to-severe dementia

The Committee noted that in May 2005 it had considered a submission from the Royal Australian and New Zealand College of Psychiatrists (RANZCP) Faculty of Psychiatry of Old Age New Zealand Branch for the funding of memantine for the treatment of severe behavioural disturbance in patients with moderate-to-severe dementia. It noted that at the time, the Committee recommended that a decision on the funding of memantine be deferred pending further review and more information being presented to PTAC.

The Committee considered that there was an unmet clinical need for patients with moderate-to-severe dementia with behavioural disturbance who responded poorly to existing treatment options. The Committee noted that currently these options are mainly antipsychotic medications, each of which has significant safety concerns.

The Committee reviewed new material provided by PHARMAC staff, including a 2006 Cochrane Review of memantine for dementia; the National Institute for Health and Clinical Excellence (NICE) technology assessment TA111 of treatments for Alzheimer's disease (updated in September 2007); the 2006 University of Southampton health technology assessment of treatments for Alzheimer's Disease used to guide the NICE TA111; published criticisms of the NICE TA111; and recent literature searches performed by PHARMAC staff.

The Committee considered that the evidence in support of memantine for the treatment of severe behavioural disturbance in patients with moderate-to-severe dementia was limited. The Committee considered that the evidence in support of the efficacy of acetylcholinesterase inhibitors for the treatment of dementia was stronger than for memantine.

The Committee noted that cost effectiveness analyses performed overseas did not support memantine as being a cost-effective treatment for dementia. The Committee noted that the overseas analyses were not able to differentiate the behaviourally disturbed patients for the purposes of the analyses.

The Committee **recommended** that the application to list memantine in the Pharmaceutical Schedule for the treatment of behavioural disturbance in moderate-to-severe dementia be declined.

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

in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.

Methylphenidate once-daily preparations (Ritalin LA and Concerta) for attention deficit and hyperactivity disorder (ADHD) – review of cost-minimisation analysis

The Committee reviewed a cost-minimisation analysis for once-daily methylphenidate preparations for the treatment of attention deficit and hyperactivity disorder (ADHD) provided by PHARMAC staff.

The Committee considered that once-daily dosing of methylphenidate is likely to have some compliance advantage compared with multiple daily dosing given that the proposed Special Authority criteria would target treatment to patients who were currently non-compliant. The Committee therefore considered that this should be factored into the analysis.

The Committee considered that once-daily methylphenidate preparations could increase compliance by up to 50% in patients who were non-compliant with doses subsequent to the initial dose. The Committee considered that this increase in compliance would translate into improvements in efficacy, although it was noted that there did not appear to be any clinical evidence to support this for methylphenidate.

The Committee noted that some evaluations of the effectiveness of stimulants consider the reduced costs of accidental injuries, hospital emergency department attendance and clinician visits as outcome measures. However, the Committee was not aware of any evidence showing that, compared with other dosage regimens, once-daily preparations of methylphenidate had a significant effect on these factors.

The Committee considered that Ritalin LA and Concerta could not be considered equivalent because of the differences in the pharmacokinetic profiles between the two brands; however, the Committee considered that the two brands were clinically similar to the extent that it would be appropriate to choose to fund one over the other based on price.

The Committee noted that due to the differences in the pharmacokinetic profiles between Concerta and Ritalin LA, patients receiving Concerta would be more likely to require a “top up” dose of short-acting methylphenidate in the morning, and that this should be factored into the analysis.

Based on all the material provided to the Committee, including recommendations from the Mental Health Subcommittee, the Committee **recommended** that a once-daily methylphenidate preparation be listed in the Pharmaceutical Schedule with a medium priority subject to the following Special Authority criteria:

Initial application only from a paediatrician, psychiatrist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 24 months for applications meeting the following criteria:

All of the following:

- 1 ADHD (Attention Deficit and Hyperactivity Disorder); and
- 2 Diagnosed according to DSM-IV or ICD 10 criteria; and
- 3 Either:
 - 3.1 Applicant is a paediatrician or psychiatrist; or

- 3.2 Both:
 - 3.2.1 Applicant is a medical practitioner and confirms that a relevant specialist has been consulted within the last 2 years and has recommended treatment for the patient; and
 - 3.2.2 Provide name of the recommending specialist
 - 4 Either:
 - 4.1 Current methylphenidate medication has not been effective due to significant administration and/or compliance difficulties; or
 - 4.2 There is significant concern regarding the risk of diversion or abuse of short-acting methylphenidate.
- Renewal only from a paediatrician, psychiatrist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 24 months for applications meeting the following criteria:
- Both:
- 1 The treatment remains appropriate and the patient is benefiting from treatment; and
 - 2 Either:
 - 2.1 Applicant is a paediatrician or psychiatrist; or
 - 2.2 Both:
 - 2.2.1 Applicant is a medical practitioner and confirms that a relevant specialist has been consulted within the last 2 years and has recommended treatment for the patient; and
 - 2.2.2 Provide name of the recommending specialist

The Decision Criteria relevant to this recommendation are: (i) *The health needs of all eligible people within New Zealand;* (ii) *The particular health needs of Maori and Pacific peoples;* (iii) *The availability and suitability of existing medicines, therapeutic medical devices and related products and related things;* (iv) *The clinical benefits and risks of pharmaceuticals;* (viii) *The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.*

Atomoxetine for treatment of attention deficit and hyperactivity disorder (ADHD) – review of cost-utility analysis

The Committee reviewed a cost-utility analysis for atomoxetine (Strattera) for the treatment of attention deficit and hyperactivity disorder (ADHD) provided by the supplier, Eli Lilly, and amended by PHARMAC staff.

The Committee noted that currently there was insufficient evidence to suggest an increased response to atomoxetine versus placebo beyond week ten.

The Committee noted that some evaluations of the effectiveness of stimulants consider the reduced costs of accidental injuries, hospital emergency department attendance and clinician visits as outcome measures. However, the Committee was not aware of any evidence showing that atomoxetine had a significant effect on these factors.

The Committee considered that the assumptions in the amended analysis were reasonable given the current evidence.

The Committee considered that it was likely that more than 25% of patients receiving ADHD medication would initially switch to atomoxetine if it was funded – perhaps as high as 50% to 70% – but that over time this would stabilise.

Based on the cost-utility analysis and previous information presented to the Committee, including the recommendations from the Mental Health Subcommittee, the Committee **recommended** that atomoxetine be listed in the Pharmaceutical Schedule with a medium priority subject to the following Special Authority criteria:

Special Authority – Retail Pharmacy

Initial application from any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

1. Once-daily dosing; and
2. Any of:
 - 2.1. Treatment with a stimulant has resulted in the development or worsening of serious adverse reactions or where the combination of stimulant treatment with another agent would pose an unacceptable medical risk; or
 - 2.2. Treatment with a stimulant has resulted in worsening of co-morbid substance abuse or there is a significant risk of diversion with stimulant therapy; or
 - 2.3. An effective dose of a stimulant has been trialled and has been discontinued because of inadequate clinical response.
3. The patient will not be receiving treatment with atomoxetine in combination with a stimulant.

Renewal from any relevant practitioner. Approvals valid for 2 years where the treatment remains appropriate and the patient is benefiting from treatment.

The Decision Criteria relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (viii) The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.*

Buprenorphine/Naloxone (Suboxone) for treatment of opiate dependence

The Committee noted that PHARMAC staff had amended the buprenorphine with naloxone (Suboxone) cost-utility analysis in order to estimate the overall cost per QALY of the proposal to fund Suboxone for both detoxification and maintenance treatment for opiate dependence.

The Committee also noted correspondence from the supplier, Reckitt Benckiser, and two medical groups (the National Association of Opioid Treatment Providers and the Aotearoa Alcohol and Other Drug Consumer Network) provided in support of the total

treatment package approach. The Committee noted that these medical groups consider that it would be inappropriate to fund Suboxone for detoxification without also funding maintenance treatment.

The Committee considered that although detoxification regimens are often unsuccessful, such that many patients may undergo several detoxifications or transfer to maintenance treatment, detoxification still exists as a discreet treatment option. As such, the Committee considered that it was appropriate to consider the funding of Suboxone for detoxification treatment and maintenance treatment separately. The Committee reiterated its previous comments and recommendations relating to the funding of Suboxone for the two indications considered separately.

The Committee considered that there was an unmet clinical need in patients who were absolutely intolerant to methadone, which members estimated to be approximately 1% of patients. The Committee noted that there was currently a mechanism in place to assess alternative funding options for these patients (ie Exceptional Circumstances).

The Committee considered that the only benefit of the naloxone component of Suboxone was to deter intravenous use (and, therefore, diversion) of buprenorphine, but noted that buprenorphine sublingual tablets were no longer available in New Zealand.

The Committee reviewed the amendments made to the cost-utility analysis. The Committee considered that the amendments to the CUA were appropriate in the context of funding Suboxone as a total treatment package. The Committee considered that, in this context, Suboxone was not considered to be relatively cost-effective (compared to methadone). The Committee **recommended** that Suboxone be listed in the Pharmaceutical Schedule as a total treatment package (subject to restrictions as previously discussed) with a low priority.

The Decision Criteria 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; (viii) The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.*

Varenicline (Champix) for smoking cessation

The Committee reviewed the proposal for varenicline (Champix) for smoking cessation as a result of post-marketing safety issues that have emerged and publication of the first head-to-head trial of varenicline versus nicotine replacement therapy (NRT).

The Committee noted that, at its May 2007 meeting, it had deferred making a recommendation on the funding of varenicline until direct head-to-head trials with NRT and longer-term efficacy and safety data were available.

The Committee noted that varenicline post-marketing data have revealed a number of clinically important adverse events related to treatment with varenicline, which have

resulted in an FDA Early Communication about ongoing safety, an EMEA (European Medicines Agency) Press Release and a Dear Doctor letter in Australia. The adverse events have included depressed mood, suicidal ideation, aggression, irrational behaviour, hallucinations, convulsions, hypersensitivity reactions and cardiovascular events.

The Committee noted that varenicline is marketed in New Zealand and is funded in a number of other countries including Australia, but that registration and funding decisions were made before any post-marketing safety data were available. The Committee also noted that, in Australia, funding is restricted to a 12-week treatment course and that only one subsidised smoking cessation product is funded per patient per year.

The Committee noted the results of the first head-to-head trial of varenicline versus NRT (Aubin et al, 2008). The Committee noted that the incremental quit rates at 52 weeks reported in the trial (compared with NRT) were 5.8% in the Primary Population Analysis ($p=0.056$) and 6.1% in the All Randomised Analysis ($p=0.040$).

The Committee noted a number of limitations with the Aubin et al study including the sample size, motivational bias due to the lack of double blinding, uncertainty regarding how patients who withdrew from treatment were accounted for, and the longer duration of treatment with varenicline than NRT. The Committee noted the inclusion of frequent counselling in the trial and considered that this would often not occur in New Zealand. The Committee also noted that the 52-week NRT quit rate of 20.3% reported in the study was higher than the quit rate reported in other NRT studies.

The Committee noted that indirect comparisons of varenicline with NRT, which the Committee had previously reviewed, had suggested a higher incremental quit rate at 52 weeks of approximately 7%. The Committee considered that the maximal 52-week incremental quit rate that would be likely to occur would be 5.8%. However, given the study's limitations and the fact that intensive counselling would often not occur in New Zealand, the Committee considered that the incremental quit rate would probably be lower in clinical practice. The Committee considered that a sensitivity analysis using the lower confidence interval limit for the incremental quit rate should be included in any cost-utility analysis to determine the impact of a lower incremental quit rate.

The Committee noted that there is no data to indicate the safety of varenicline in combination with other smoking cessation products, in pregnancy, or in patients under the age of 18. The Committee considered that varenicline should therefore not be used in combination with other smoking cessation products, in pregnancy, or in patients under the age of 18.

The Committee considered that more post-marketing data is required to clarify the risk-benefit profile of varenicline in clinical practice, that the datasheet required updating to include the post-marketing safety signals, that the drug should be a mandatory inclusion in the Intensive Medicines Monitoring Programme (IMMP), and that any listing should be restricted to 12 weeks treatment per patient with no more than one funded treatment course per year. The Committee further considered that PHARMAC staff should write to Medsafe regarding its comments about the datasheet and IMMP monitoring.

The Committee considered that safety concerns were greater than previously appreciated and that the incremental effectiveness of varenicline over NRT to be less

than previously considered. The Committee **recommended** that varenicline not be listed on the Pharmaceutical Schedule due to safety concerns and incomplete information on clinical effectiveness. The Committee also **recommended** that any review of the safety of varenicline should not be performed until at least another year of post-marketing data is available. The Committee therefore **recommended** deferring the listing of varenicline pending additional information regarding the safety of varenicline and further clinical trial results demonstrating the incremental effectiveness of varenicline compared with NRT.

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

12 months clopidogrel treatment in patients with a drug-eluting stent

The Committee considered three independent applications for extending access to clopidogrel following drug-eluting stent (DES) implantation from the current six months to 12 months so that it would be consistent with international guidelines. These applications were from [withheld under section 9(2)(a) of the OIA] and Sanofi-Aventis.

The Committee reviewed an advisory article from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, the American College of Surgeons, and the American Dental Association authored by Grines et al (2007) and published in both the Journal of the American College of Cardiology 2007; Vol 49 No 6; and Circulation; 2007; 115. The Committee also reviewed the relevant information that was cited in this article.

The Committee reviewed the recommendations for the use of oral antiplatelet therapy contained in the American College of Cardiology, American Heart Association, and Society for Cardiovascular Angiography and Interventions 2005 Guideline Update for Percutaneous Coronary Intervention. The Committee also reviewed the relevant information that was cited in this article.

The Committee noted that the above guidelines recommend that clopidogrel be used for 12 months following a DES. The Committee also noted that it is recommended that if compliance with 12 months clopidogrel is not expected then the use of a bare metal stent (BMS), instead of a DES, should be considered.

The Committee noted that concerns with DES include late stent thrombosis and an associated high incidence of MI or mortality. The Committee also noted that there are concerns with BMS including a high incidence of acute and subacute stent thrombosis and re-stenosis.

The Committee noted that even though DES were approved for selected indications they have become widely used for off-label indications in the United States. The Committee also noted that there appears to be a slight increase in late stent thrombosis with their use and that this is possibly related to their increased off-label use. The Committee also noted that DES are considerably more expensive than BMS, and that a cost-utility

analysis comparing DES with BMS performed by PHARMAC staff concluded that DES are not as cost-effective as BMS. The Committee also noted a recent NICE recommendation that DES should be used in long lesions and small vessels only if the cost differential between DES and BS is less than £300. The Committee considered that there may be a place for DES especially in patients with long lesions or small vessels if DES could be procured at a cheaper price.

The Committee noted that literature was beginning to accumulate suggesting that a rebound effect may occur when discontinuing clopidogrel, and considered that this evidence should be assessed to provide guidelines on how to discontinue clopidogrel.

The Committee noted the study by Eisenstein et al (2007), which assessed the relationship between clopidogrel use and long-term clinical outcomes in patients receiving DES and BMS. The Committee considered that the study had the following limitations: it is an observational cohort study with patient groups that are not comparable, patients with a previous PCI or CABG are excluded, patients with both BMS and DES are classified as DES patients, there is no information regarding the use of DES off-label, there are differences in baseline characteristics such as CHF (9.6% vs 14.5%), a number of patients are excluded (18% and 24% at 6 months and 64% and 37% at 12 months), clopidogrel use is based on patient recall, a considerable number of patients started clopidogrel during the study period, there is a lack of events in the DES clopidogrel arm at 12 months (likely to be due to chance), bleeding risks of the patients are not recorded, and the definition of MI is not clear. The Committee therefore considered that overall the study was of poor quality.

The Committee reviewed a number of other references cited by Grines et al (2007) and the American College of Cardiology, American Heart Association, and Society for Cardiovascular Angiography and Interventions 2005 Guideline Update for Percutaneous Coronary Intervention. Some of the studies indicated that DES are associated with increased thrombotic risk; however, the Committee noted that the studies used different patient populations and none of them addressed the specific question of the appropriate duration of clopidogrel use after DES.

Overall, the Committee concluded that there was no good (level 1) evidence to determine the optimum duration of clopidogrel therapy following DES. The Committee also noted that there could be an increased risk of moderate to severe bleeding of up to 2% per year associated with long-term use of clopidogrel. The Committee considered that an appropriately designed clinical trial would be required to determine the optimum duration of clopidogrel therapy following DES.

The Committee noted that the number of patients in New Zealand using DES was estimated to be small (20-30% of total stent patients) and that any decision to extend clopidogrel access to 12 months would have a small budgetary impact.

The Committee **recommended** that access to clopidogrel be extended from six months to 12 months following drug-eluting stent placement with a low priority. The Committee considered that this recommendation was appropriate despite there being no good supporting evidence, as the fiscal impact would be low and there is a high prevalence of MI or death after late stent thrombosis.

The Committee considered that PHARMAC should consider writing a letter to the Cardiac Society about appropriate guidelines for use of DES and anti-thrombotic therapy in New Zealand, in light of evolving evidence and recent NICE recommendations.

The Decision Criteria relevant to this recommendation are: (i) *The health needs of all eligible people within New Zealand; 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.*

Clopidogrel – review of Special Authority criteria

The Committee considered a number of suggested alterations to the clopidogrel Special Authority criteria from [withheld under section 9(2)(a) of the OIA] and Sanofi-Aventis.

[withheld under section 9(2)(a) of the OIA]

The Committee considered a suggestion to alter the acute coronary syndrome definition (referred to in the “aspirin allergic patients”, the “aspirin tolerant patients”, and “aspirin naïve patients” parts of the current Special Authority criteria) so that it is more consistent with current international practice (ACC/ESC consensus document and definitions) by changing the current criteria to a proposed criteria as follows.

Current criteria

Experienced an acute myocardial infarction

OR

Experienced an episode of pain at rest of greater than 20 minutes duration due to coronary disease that required admission to hospital for at least 24 hours

OR

Had a troponin T or troponin I test result greater than the upper limit of the reference range

Proposed criteria

Troponin-positive STEMI or non-STEMI acute coronary syndrome

OR

Troponin-negative acute coronary syndrome, with chest pain of > 20 minutes duration and hospital admission > 24 hours

The Committee noted that this definition change would not affect the inclusion of the revascularisation criteria or other criteria in these patient groups and **recommended** that the change be made.

The Committee considered a suggestion to alter the “patients awaiting revascularisation” criteria slightly by requiring Acute Coronary Syndromes as follows:

Current criteria

The patient is on a waiting list or active review list for stenting, coronary artery bypass grafting, or percutaneous coronary angioplasty following acute coronary syndrome

Proposed criteria

Troponin-positive or troponin-negative acute coronary syndrome
AND
Is on a waiting list for surgical or percutaneous revascularisation

The Committee considered that access would be similar under either criteria and considered that the current criteria should remain due to clinician familiarity.

The Committee considered a suggestion to alter the current criteria for patients who experience an additional vascular event following the cessation of clopidogrel so that:

- If an additional event occurs within six months of clopidogrel discontinuation then the patient gets lifetime clopidogrel approval.
- If an additional event occurs more than six months after clopidogrel discontinuation then the patient would get another six or three months of clopidogrel.

Current criteria – lifetime approval

While on treatment with aspirin the patient has experienced an additional vascular event following the recent cessation of clopidogrel

Proposed criteria – lifetime approval

The patient has had < 6 months after discontinuing clopidogrel a:

Troponin-positive STEMI or non-STEMI acute coronary syndrome
OR

Troponin-negative acute coronary syndrome, with chest pain of > 20 minutes duration and hospital admission > 24 hours

Proposed criteria – 6 months approval

The patient has had > 6 months after discontinuing clopidogrel a:

Troponin-positive STEMI or non-STEMI acute coronary syndrome
OR

Troponin-negative acute coronary syndrome, with chest pain of > 20 minutes duration and hospital admission > 24 hours

The Committee noted that both the Cardiovascular Subcommittee (October 2004), and PTAC (November 2004 and May 2006) had previously considered that a two-week period for any additional event was appropriate and that six months was too long. The Committee **considered** that the current criteria allowed more flexibility than was being proposed and that they were appropriate.

The Committee considered a suggestion that the criteria “revascularisation procedure” be replaced with the criteria “coronary, carotid or peripheral arterial revascularisation”. The Committee **considered** that the current criteria wording was appropriate.

Sanofi-Aventis

The Committee considered a request that clopidogrel access be extended from the current three months to six or twelve months for medically managed patients following

an acute coronary syndrome so that patient access would be consistent with the ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction. The Committee noted that it had considered the duration of clopidogrel treatment post acute coronary syndrome at its August 2004 meeting. The Committee noted that it was not aware of any new data and that it had not been provided with any. The Committee considered that most of the benefit with clopidogrel occurred within the first three months and that a three-month treatment course was the most cost-effective way of funding clopidogrel in this setting. The Committee therefore **recommended** that there be no change to the criteria relating to the time period following an acute coronary event.

The Committee considered a request that the definition of aspirin allergic patients in the clopidogrel Special Authority be altered so that it is consistent with the dipyridamole intolerance criteria as follows:

Current definition

Aspirin allergy is defined as a history of anaphylaxis, urticaria or asthma within 4 hours of ingestion of aspirin, other salicylates or NSAIDs

Proposed definition

Aspirin intolerant patients are defined as those with aspirin induced asthma, urticaria, or anaphylaxis, or those with significant aspirin induced bleeding, excluding bruising

The Committee noted that the major difference between the two criteria is the exclusion/inclusion of aspirin induced gastrointestinal bleeding. The Committee noted that the evidence was inconclusive as to whether clopidogrel had any advantages over aspirin when used in conjunction with a proton pump inhibitor following an episode of aspirin-induced gastrointestinal bleeding. The Committee **recommended** that the current criteria remain but that it would be appropriate to review this decision if evidence supporting any gastro-protective effect of clopidogrel is supplied.

Other

The Committee considered whether the renewal criteria for “aspirin tolerant patients” should enable patients who experience an additional vascular event while being on clopidogrel to be able to access clopidogrel for life. Members noted that the current criteria provide lifetime approval to patients who, while on aspirin, experience an additional vascular event following the recent cessation of clopidogrel.

Current renewal criteria for aspirin tolerant patients

While on treatment with aspirin the patient has experienced an additional vascular event following the recent cessation of clopidogrel

Proposed renewal criteria for aspirin tolerant patients

While on treatment with aspirin the patient has experienced an additional vascular event following the recent cessation of clopidogrel
OR

While on treatment with clopidogrel the patient has experienced an additional vascular event

The Committee noted that the proposed criteria are appropriate and **recommended** that access be widened accordingly.

The Committee looked at other potential areas for the use of clopidogrel. The Committee considered that high-risk patients presenting with transient ischaemic attacks may benefit from a short course of clopidogrel in terms of preventing strokes. The Committee considered that it would like to review evidence for this indication at a later date.

The Committee reiterated its previous recommendation that the Special Authority be removed from the dipyridamole listing on the Pharmaceutical Schedule to reduce prescriber administration, subject to budgetary constraints.

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

Ciprofloxacin/Hydrocortisone (Ciproxin HC) for treatment of otitis media with a perforated tympanic membrane (TM) and associated conditions such as chronic suppurative otitis media (CSOM)

The Committee reviewed applications from [withheld under s9(2)(a) of the OIA] and the New Zealand Society of Otolaryngology Head and Neck Surgery for the listing of ciprofloxacin 0.2% with hydrocortisone 1.0% ear drops (Ciproxin HC) on the Pharmaceutical Schedule for the treatment of otitis media with a perforated tympanic membrane (TM) and associated conditions such as chronic suppurative otitis media (CSOM).

The Committee noted that an earlier application for the funding of ciprofloxacin with hydrocortisone ear drops was made in 2003 and at that time the Antibiotic Subcommittee recommended declining the application in light of concern about quinolone resistance and insufficient information supplied to validate the statements made in the application.

The Committee noted that the New Zealand Society of Otolaryngology Head and Neck Surgery and [withheld under s9(2)(a) of the OIA] were concerned about the ototoxic potential of currently funded aminoglycoside ototopical agents when used to treat middle ear

infections in the presence of a non-intact tympanic membrane. Members noted that both applicants suggest ciprofloxacin with hydrocortisone ear drops are non-ototoxic and should be funded.

The Committee reviewed the evidence provided by both applicants and further evidence regarding efficacy of ototopical quinolones, ototoxicity of aminoglycoside ear drops and antibiotic resistance from the use of ototopical agents.

Members considered that evidence for efficacy of ciprofloxacin with hydrocortisone ear drops in otitis media with perforated TM was limited. The Committee reviewed one randomised, double blind, controlled trial (*Couzos et. al. MJA, 2003*) comparing topical 0.3% ciprofloxacin with framycetin (0.5%), gramicidin and dexamethasone (Sofradex) for CSOM in 147 children aged 1-14 years. A highly significant absolute difference of 24.6% in clinical cure (resolution of otorrhoea) was reported in favour of ciprofloxacin compared with Sofradex (76.4% vs 51.8%; P=0.009). However, only those children who had a post-treatment assessment (n=111) were included in the statistical analysis; an intention-to-treat analysis was not undertaken. There was no difference in TM perforation size or hearing.

The Committee noted further evidence regarding the efficacy of topical quinolones (without steroid) from two Cochrane reviews by Macfadyen et.al., 2005 and Macfadyen et.al., 2006 (*Macfadyen et.al., The Cochrane Library, 2007*). The reviews indicated that topical quinolones were superior to systemic antibiotics and topical antiseptics but the difference between topical quinolones and non-quinolones was unclear. The reviewers considered that the studies evaluated in the reviews were of varying methodological quality and poorly reported, and while the evidence presented related to short-term clearance of aural discharge, long-term outcomes and safety were unclear.

The Committee noted the position statement from the New Zealand Society of Otolaryngology Head and Neck Surgery on the use of potentially ototoxic ear drops. Members considered that the statement is consistent with Australian and American guidelines and that there is a small risk of ototoxicity (in the order of 1:1000 to 1:10,000) from the use of ototopical aminoglycosides in situations where there is a direct pathway to the middle ear. Members also noted that the Society recommends, where possible, avoiding the use of potentially ototoxic ear drops in the presence of a non-intact TM.

The Committee reviewed further evidence regarding ototoxicity of aminoglycoside ear drops from a review by Roland et al (*Otolaryngology – Head and Neck Surgery, 2004*) and Matz et al (*Otolaryngology – Head and Neck Surgery, 2004*) and noted that the evidence was largely from animal studies with some case reports in humans. Members noted that there are anatomical differences between the human ear and experimental animal ear and, as such, data needs to be extrapolated with caution. Members also considered that ototoxicity in humans may be underappreciated because the earliest and most severe auditory manifestations may occur at higher frequencies which are usually not tested in humans; the vestibular manifestations, if unilateral, may be subtle; and some damage may be misattributed to the condition.

The Committee also noted an opinion from [withheld under s9(2)(a) of the OIA], consultant otolaryngologist regarding ototoxicity of ototopical ear drops. The Committee noted [withheld under s9(2)(a) of the OIA]'s views on the use of ototoxic ears drops and [withheld under s9(2)(a) of the OIA]'s concern around the safety of quinolone ear drops and antibiotic

resistance. The Committee noted that there was no evidence provided in support of [withheld under s9(2)(a) of the OIA]'s view. The Committee agreed that there was insufficient evidence regarding the safety of quinolone ear drops when used in the presence of a non-intact TM.

The Committee noted that quinolone resistance has been raised as a concern because of increasing quinolone use. The Committee reviewed evidence from a review by Weber et al (*Otolaryngology – Head and Neck Surgery, 2004*) on development of resistance with the use of ototopical antibiotics. The Committee noted that there was grade B evidence to indicate that no significant antibiotic resistance develops from use of ototopical antibiotics. Members noted further support for this from a review article by J Kline (*Amer J Managed Care, 2002*), which recommends using ototopical antibiotics rather than systemic antibiotics for treating middle ear infections to reduce the risk of developing bacterial resistance. The Committee also noted the opinion of [withheld under s9(2)(a) of the OIA], a member of the Anti-infective Subcommittee, who considered that the use of ciprofloxacin ear drops would provide relatively minor selection pressure for emergence of resistant organisms.

The Committee acknowledged the New Zealand Society of Otolaryngology Head and Neck Surgery's concern around the medico-legal risk from the use of potentially ototoxic ear drops in treatment of otitis media in the presence of a non-intact TM. However the Committee noted that potentially ototoxic ear drops had been used, off-label, to treat middle ear infections in the presence of a non-intact TM for many years and considered that the risk of ototoxicity from aminoglycoside ear drops was low.

The Committee considered that there may be an unmet need for a safer alternative in certain populations such as low socio-economic, Maori, and Pacific Island people in whom chronic middle ear conditions are more prevalent.

However, the Committee considered that there was insufficient evidence to suggest ciprofloxacin with hydrocortisone ear drop were a safer alternative to use in the presence of a non-intact TM. The Committee noted that the manufacturer of ciprofloxacin with hydrocortisone ear drops states that the safety and efficacy of ciprofloxacin with hydrocortisone ear drops have not been studied in the presence of a perforated tympanic membrane and ciprofloxacin with hydrocortisone ear drops are, therefore, contraindicated in patients with known or suspected perforation, or where there is a risk of perforation of the tympanic membrane.

The Committee **recommended** that the application for funding of ciprofloxacin 0.2% with hydrocortisone 1.0% ear drops (Ciproxin HC) be declined because of insufficient evidence to suggest that they were more efficacious than currently funded ear drops or were safer to use in the presence of a non-intact TM.

The Committee also suggested that the applicants approach the manufacturer for evidence on safety of using ciprofloxacin with hydrocortisone ear drops to treat otitis media in the presence of a TM perforation and if applicable, a change in the manufacturer's data sheet recommendation to reflect this.

The Decision Criteria relevant to this recommendation are: (i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical

devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (vii) The direct cost to health service users, and (viii) The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.

Brimonidine tartrate (Alphagan P) for treatment of glaucoma

The Committee reviewed an application from Allergan (NZ) for the funding of brimonidine tartrate 0.15% with Purite eye drops (Alphagan P) for the treatment of glaucoma.

The Committee noted that Alphagan P contains 0.15% brimonidine tartrate, an alpha 2 adrenergic agonist, in a base preserved with Purite instead of the commonly used preservative benzalkonium chloride. Purite is suggested to reduce the risk of corneal disruption and inflammation when compared with benzalkonium chloride and enhance the ocular penetration of brimonidine by increasing the pH.

The Committee considered that brimonidine was regarded as a third- or fourth-line agent, after beta-blockers and prostaglandin analogues, for treating glaucoma. The Committee noted that 0.2% brimonidine tartrate eye drops are currently funded.

The Committee noted that the supplier claims that Alphagan P is as effective as brimonidine 0.2% eye drops but has a superior safety and tolerability profile, in particular, reduced ocular allergy. Members noted that the supplier argues that a reduction in ocular allergies results in fewer discontinuations, which reduces costs associated with management of patients who fail treatment.

The Committee reviewed three studies, Study 190342-007, Study 190342-008 and Study 190342-017 provided by the supplier as evidence to support its claim. Members noted that Study 190342-007 and Study 190342-008 were multi-centre, double-blind, randomised active-control, parallel group 12-month studies that showed Alphagan P and brimonidine 0.2% eye drops had similar efficacy. Members considered that in these two studies treatment was administered three times a day, which is inconsistent with recommended twice daily dosing. Members also noted that Study 190342-017 was a short-term (three month) phase III b trial that showed no significant difference in efficacy and incidence of any adverse events between Alphagan P and brimonidine 0.2% eye drops.

The Committee also noted that of the treatment-related adverse effects rates, the rate of allergic conjunctivitis was statistically different between the Alphagan P group and the brimonidine 0.2% group in Study 190342-007 but not in Study 190342-008. In Study 190342-008, the difference in rates of treatment-related oral dryness between the groups was statistically significant. The Committee noted that pooled analysis of intention-to-treat data of Studies 190342-007 and 190342-008 (*Katz, J Glaucoma, 2002*) showed statistically significant differences in the rates of allergic conjunctivitis, oral dryness, conjunctival hyperaemia and eye discharge. The Committee considered that it was difficult to interpret the clinical significance of this difference as pooled analysis of patient discontinuation rates resulting from adverse events that led to discontinuation from study were not statistically different between the groups.

The Committee considered that the three times a day study dosing (as opposed to the recommended twice daily dosing) could have accounted for the higher overall rates of treatment-related side effects. The Committee also considered that only one of the three studies showed a statistically significant difference in the rates of allergic conjunctivitis.

The Committee considered that Alphagan P had the same or similar therapeutic effect as brimonidine tartrate 0.2% eye drops and that these products could be reference priced. Therefore, the Committee **recommended** that Alphagan P be listed on the Pharmaceutical Schedule only if it was cost-neutral compared with brimonidine tartrate 0.2% eye drops.

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

Goserelin acetate (Zoladex) for treatment of uterine fibroids

The Committee considered an application from AstraZeneca for the listing of goserelin acetate (Zoladex) for treatment of uterine fibroids. Goserelin is currently listed in the Pharmaceutical Schedule for the treatment of breast cancer, prostate cancer, endometriosis and precocious puberty.

Members noted that goserelin is a gonadotrophin-releasing hormone (GnRH) analogue that reduces serum oestradiol levels in women. The reduction in oestradiol leads to decreased growth of uterine fibroids, improved haematological status and reduction of symptoms. Administration of a GnRH-analogue is intended for a short course (maximum three months) with the goal of reducing the fibroid size pre-operatively, thus improving the ease of surgery.

Members noted the presence of leuprorelin (another GnRH-analogue) and a number of other pre-surgical hormonal-based pharmacological treatments for uterine fibroids, some with apparent good evidence of effect.

Members noted that the time restriction on GnRH-analogue treatment is important, as long-term treatment leads to adverse effects, especially bone resorption. It is also important that treatment is immediately pre-surgery as cessation of treatment may lead to rebound growth of fibroids to pre-treatment size within six months.

The Committee reviewed two studies that most closely resembled the proposed indication. A randomised, placebo-controlled study by Lumsden et al (Br J Obstet Gynecol May 1994;101:438-442) investigated the effect of goserelin, given by monthly injection for three months pre-TAH (total abdominal hysterectomy) to 71 women with

uterine fibroids, on pre-operative symptoms, difficulty of operation and operative blood loss.

Members noted that the uterine fibroid size was larger in the placebo group, which could have influenced some of the findings. At time of operation uterine fibroid size had decreased significantly (-24%) in the goserelin group compared to the placebo group (+3%). Pelvic symptom scores were significantly less in the goserelin group. There was a significant rise of haemoglobin in the goserelin group and 80% of women in this group were rendered amenorrhoeic. There was a significant difference in median operative blood loss between the goserelin group (187 ml) and the placebo group (307 ml) but no significant difference in operative duration, post-operative complications or duration of hospital admission between the two groups. More women in the goserelin group experienced night sweats and hot flushes than in the placebo group.

Members also reviewed a multinational, multicentre, prospective, randomized, double-blind study by Benagiano et al (Fertil Steril 1996;66:223-9) comparing effects of goserelin treatment with or without iron, and iron alone. One hundred eighty-five women with uterine fibroids were randomized to goserelin 3.6 mg once monthly + placebo iron, goserelin 3.6 mg once monthly + iron 600 mg od or only iron 600 mg od. The results showed a significant decrease in uterine fibroid volume in both goserelin groups, significant differences in haemoglobin levels (1g/dl between goserelin + iron and iron, 2.6 g/dl between goserelin + iron and goserelin, 1.6 g/dl between iron and goserelin) and significant reduction in pelvic pain in both goserelin groups. Operative blood loss was significantly less in goserelin only versus both iron only and goserelin plus iron. There was no significant difference in duration of surgery, ease of surgery and length of hospital stay between the groups.

The Committee noted that the New Zealand guidelines (NZGG 2000) concluded that GnRH-analogues can be recommended for pre-operative use in women with a greatly enlarged uterus, pre-operative anaemia or when a midline rather than a transverse incision would be planned. In addition some women undergoing hysterectomy would be able to avoid an incision as their uterus may be able to be removed via the vaginal route.

Members noted that the prevalence rate for fibroids (40%) used by the supplier seems reasonable, but that treatment rates were based on United States data and might be higher in New Zealand.

The Committee discussed the cost-effectiveness of goserelin in uterine fibroids. The submission included a brief willingness-to-pay economic analysis based effectively on one paper, which was not included. Some other cost-effectiveness analyses were included as abstracts only. The Committee considered the models and assumptions used in the supplier's analysis needed further review.

The Committee considered that the proposed Special Authority criteria needed to be better targeted and the treatment be compared to alternative treatment options in terms of efficacy, safety and cost effectiveness.

The Committee **recommended** that the application be referred to the Hormone and Contraceptive Subcommittee to consider the role of goserelin in the overall pre-operative pharmacological treatment of uterine fibroids, and that PHARMAC staff subsequently

undertake further work on goserelin's cost-utility in the context of its overall place in treatment for uterine fibroids.

Leflunomide – review of Special Authority

The Committee considered an application for widening access of leflunomide to include rheumatic disorders other than rheumatoid arthritis (RA). The Committee noted that the current Special Authority for leflunomide restricted access to patients with RA.

The Committee noted that at its November 2007 it had recommended that the Special Authority Criteria for leflunomide be reviewed with urgency following the receipt of a submission from the New Zealand Rheumatology Association (NZRA) regarding new treatments for patients with active psoriatic arthritis (PsA).

The Committee reviewed a multinational, double-blind, randomized, placebo-controlled clinical trial (*Arthritis Rheum.* 2004;Jun:50(6):139-150) where 190 patients with active PsA and psoriasis were randomised to leflunomide 100 mg daily for three days and then 20 mg once daily or placebo for six months. The Committee noted that the results of the trial indicated that leflunomide was significantly superior to placebo with 59% of patients in the treatment group classified as responders by the Psoriatic Arthritis Response Criteria (PsARC) compared with 30% in the placebo group. Significantly more patients in the leflunomide group reached a modified ACR20 response (36.3% compared to 20%). In addition, significantly more patients in the leflunomide group demonstrated improvement of PASI scores (change in the extent and severity of psoriasis lesions). The most common side-effects in the leflunomide group were diarrhoea and increased ALT levels.

The Committee reviewed two trials regarding treatment of ankylosing spondylitis with leflunomide (*Ann Rheum Dis.* 2005;64:1761-1764, *Ann Rheum Dis.* 2005;64:124-126). The Committee noted that these trials indicated that leflunomide is not effective for treatment of axial symptoms; however, patients with peripheral arthritis improved significantly.

The Committee noted that leflunomide is associated with considerable adverse effects and is contraindicated in pregnancy (category X). Therefore it is unlikely to continue to be used in patients who are not benefiting from treatment.

The Committee noted that there is an unmet need for treatment in patients with severe PsA who have failed treatment with methotrexate and sulfasalazine.

The Committee considered that the number of patients who are likely to access leflunomide following widening of the Special Authority is likely to be less than 250.

The Committee considered a letter from [withheld under s9(2)(a) of the OIA] NZRA, summarising its view on the consequences of a Special Authority removal.

The Committee noted that leflunomide is also an option for treating psoriasis and that removal of the Special Authority is likely to lead to some use for this patient group. The Committee noted that [withheld under s9(2)(a) of the OIA] considered that this demand is likely to be small.

The Committee noted the CUA provided by PHARMAC staff. The Committee considered that the analysis was appropriate, and that the result compared favourably with other pharmaceuticals that were under consideration for funding.

The Committee **recommended** that the wording “Rheumatoid” in the Special Authority be changed to “Inflammatory”. The Committee gave this recommendation a high priority.

The Decision Criteria 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, 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*.

Multivitamin for children on ketogenic diet

The Committee considered an application from [withheld under s9(2)(a) of the OIA] on behalf of the New Zealand Chapter of the International League Against Epilepsy. The application requests widening access to multivitamin supplements and minerals (specifically Ketovite tablets, Ketovite liquid and Metabolic Mineral Mixture) to include children on the ketogenic diet for epilepsy, with applications restricted to paediatric or adult neurologists.

The Committee noted that these products are currently available on the Pharmaceutical Schedule but restricted to patients with inborn errors of metabolism.

The Committee reviewed a study from Johns Hopkins Medical Institutions (Pediatrics. 1998;102:1358-1363). The study reported outcomes of 150 children with refractory epilepsy three, six and 12 months after initiation of the ketogenic diet. Continuation of the diet was 83% at three months, 71% at six months and 55% at one year. Members noted that by 12 months, 11 children (7%) were seizure-free and a further 30 children (20%) had a 90% or greater decrease in seizures. Adverse effects were reported for seven children with kidney stones and five children with acidosis and vomiting.

The Committee considered a follow-up study (Pediatrics. 2001;108:898-905) showing that 39% of the children remained on the diet for two years and 20% for three years. Three to six years after initiation of the diet 13% of the children were seizure free and another 14% had a 90% decrease in seizures. Many patients were on fewer medications than at outset or were no longer using medications.

The Committee noted a review of the ketogenic diet (Pediatrics. 119.3 (March 2007):p535(9)), describing the history of the diet and the increase in interest since 1996. Additional adverse effects reported were decreased bone density and dyslipidaemia, the long-term consequences of which are unknown.

The Committee noted that the need for vitamin and mineral supplements was not documented in the application, even though supplementation is probably important for patients on a highly restricted diet. There was also a lack of dietician opinion regarding the necessity of the supplements, specifically the detailed dietary protocol from Johns Hopkins wasn’t provided with application.

Members noted that the additional cost of treatment would be low. The estimated patient number of 40 was considered reasonable.

The Committee **recommended** widening access of the multivitamins and minerals to include children on the ketogenic diet, provided that this recommendation is agreed to by the Special Foods Subcommittee.

Folic acid supplementation in pregnancy

The Committee reviewed an application from the Ministry of Health to change the subsidised folic acid dose listed in the Pharmaceutical Schedule for the prevention of neural tube defects (NTD) from a 0.8 mg tablet to a 0.4 mg tablet.

The Committee noted a number of trials investigating the effect of folic acid on the incidence of NTD including Czeizel et al (1992), Wald et al on behalf of the MRC Vitamin Study Research Group (1991), and Berry et al (1999).

The Committee noted that Czeizal et al (1992) conducted a randomised controlled trial where 2104 women received a vitamin supplement containing 0.8 mg of folic acid and 2052 women received a trace element supplement (not containing folic acid). The Committee noted that the NTD were significantly less prevalent ($p=0.029$) in babies of women receiving folic acid ($n=0$) than in babies of women not receiving folic acid ($n=6$).

The Committee noted that Wald et al (1991) reported the results of the MRC Vitamin Study Research Group, which performed a randomised double-blind study to determine whether supplementation with 4 mg of folic acid could prevent neural tube defects in women with a previous pregnancy affected by a NTD. The Committee noted that out of 1031 women who were not pregnant at randomisation, 5 of 514 (1.0%) taking folic acid until 12 weeks of pregnancy, and 18 of 517 women (3.5%) not taking folic acid, had neural tube defects (relative risk of 0.28; 95% CI 0.11 to 0.75).

The Committee noted that Berry et al (1999), in a cohort study of 250,000 Chinese women, found that a daily dose of 0.4 mg folic acid during the preconceptional period reduces the incidence of NTD in areas of both high and low NTD frequency.

The Committee noted that there were no studies available which compared the efficacy of a 0.4 mg, a 0.5 mg, or a 0.8 mg dose of folic acid for the prevention on NTD, and that there is no evidence available to indicate which dose is the most appropriate.

The Committee noted that none of the trials reported any serious adverse events.

The Committee noted that fortification of bread with folate is becoming mandatory. The Committee considered that fortification was essential to provide some folic acid to women who do not take folic acid tablets and become pregnant.

The Committee noted that the recommended upper level of daily intake for folate is 1.0 mg and that this may be exceeded in some women if they consume fortified bread and take a 0.8 mg tablet daily. The Committee noted that excessive folic acid can result in neurological damage in those who are already vitamin B12 deficient but that vitamin B12

deficiency was rare in women of child-bearing age. The Committee noted that there was no evidence to suggest that a 0.8 mg dose is a risk in this population group and considered that a dose of more than 1.0 mg would not result in any adverse events. The Committee also considered that some women would not take a tablet every day and therefore a 0.8 mg tab would ensure an appropriate dose for these women, that some women may not eat the fortified bread, and that if a women was concerned that they are taking too much folate then they could take a 0.8 mg tablet on alternate days.

The Committee considered that spina bifida is a devastating disease and that the 0.4 mg dose may not provide a complete protective effect with variable compliance, which is likely outside trials.

The Committee considered that it is preferable to take more folic acid than less and therefore **recommended** that the 0.8 mg dose of folic acid is maintained as the low dose of folic acid available on the Pharmaceutical Schedule. Therefore the Committee declined the application to change the listed folic acid tablet strength to 0.4 mg.

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

Insulin glargine (Lantus SoloStar) for diabetes mellitus

The Committee considered an application from Sanofi Aventis for a new disposable insulin delivery device (Lantus SoloStar) for insulin glargine to be listed on the Pharmaceutical Schedule at the same price, and under the same restrictions, as the current insulin glargine cartridges.

The Chair tabled the Chicago Athenaeum Museum of Architecture and Design award that the supplier had sent following its initial application.

Members noted the company's claims that the new delivery device incorporated a number of new and improved features compared with existing insulin pen devices. These included simplicity of use, reduced force requirement to deliver the injection, shorter dial extension than Levemir FlexPen, a maximum deliverable dose of 80u (compared with 60u for FlexPen and 21 to 42u for Autopen 24), easy-to-read dose display, and the strength and robustness of the device.

The Committee considered the evidence in the application that considered acceptance, usability and preference of comparable insulin delivery devices. Members noted that the results were positive in these areas for the SoloStar device.

The Committee noted that the company proposed to introduce SoloStar gradually; however, the Committee considered that the uptake of the new device would be fast.

The Committee considered that the SoloStar's larger maximum deliverable dose may result in patients using larger doses over time and subsequently lead to increased expenditure.

Members noted that the user instructions advise that a new needle be attached before each use, and that the needle be discarded after each use, whereas needle re-use is typical in New Zealand. Members noted that this may lead to blockage problems and could lead to wastage. Members noted that the submission stressed the need to always have a needle attached when using the device to avoid putting it under pressure. Members requested that PHARMAC staff seek advice from the supplier, as to whether using the device without a needle (or with a blocked needle) can result in permanent damage to the device and lead to wastage.

The Committee **recommended** that the application be referred to the Diabetes Subcommittee of PTAC for consideration. Members considered that, subject to the Diabetes Subcommittee of PTAC agreement, the Committee did not object to the listing of SoloStar on the Pharmaceutical Schedule.

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

Acetylcholinesterase inhibitors for the treatment of Alzheimer's disease

The Committee noted that it had previously reviewed applications to list the acetylcholinesterase inhibitors (AChEIs) donepezil, galantamine and rivastigmine on the Pharmaceutical Schedule and had recommended listing these treatments under Special Authority criteria with a low priority. The Committee noted that in 2004 PHARMAC's Board had declined funding for these agents.

The Committee reviewed material provided by PHARMAC staff, including the AD2000 study (a randomised, placebo-controlled, double-blind trial of donepezil in Alzheimer's disease) and associated commentary; a 2006 Cochrane Review of AChEIs for Alzheimer's disease; a 2006 Cochrane Review of donepezil for Alzheimer's disease; the National Institute for Health and Clinical Excellence (NICE) technology assessment TA111 of treatments for Alzheimer's disease (updated in September 2007); the 2006 University of Southampton health technology assessment of treatments for Alzheimer's disease used to guide the NICE TA111; published criticisms of the NICE TA111; and recent literature searches performed by PHARMAC staff.

The Committee noted that although the AD2000 trial showed cognitive and functional benefits from donepezil compared with placebo, the design of, and patient accruals to the trial had been widely debated. The Committee noted that the Cochrane Review of

AChEIs considered that the trial's limitations made it unwise to base important funding decisions on its results.

The Committee considered that the 2006 Cochrane Review supported small but significant effects from AChEIs on cognition, global rating, behaviour and function compared to placebo in 3–6 month trials. The Committee noted that the review concluded that AChEIs are effective for mild to moderate dementia.

The Committee noted that NICE recommended donepezil, galantamine and rivastigmine as options in the management of patients with Alzheimer's disease of moderate severity only, and that NICE considered that the three agents were equally effective. The Committee considered that although the recommendation appeared to make sense on the basis of cost-effectiveness analysis, it may be more clinically appropriate for the AChEIs to be given earlier in the disease process.

The Committee noted that there were few new studies published since it last considered the AChEIs, and considered that it was unlikely that there would be significant new data to help guide a funding decision at this stage.

The Committee noted that Alzheimer's disease is a very disabling disease and has a significant impact on the quality of life of caregivers. The Committee also noted the potential for important gains in caregivers' quality of life resulting from improvements, or delays in deterioration, in patients treated with AChEIs.

The Committee **recommended** that PHARMAC perform a budget impact analysis and present this to the Committee.