

PTAC meeting held 19 & 20 February 2009

(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 that contain a recommendation in relation to an application 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.

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- protect the privacy of natural persons (section 9(2)(a))
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1 Record of PTAC Meeting held 6 & 7 November 2008

- 1.1 The Committee reviewed the record of the PTAC meeting held on 6 & 7 November 2008 and noted the Low molecular weight heparin Discretionary Community Supply criteria and **recommended** the following change – paragraph 10.5: Replace “For a maximum of 14 days prophylaxis treatment in high-risk patients post-pelvic, colo-rectal and major orthopaedic surgery” with “For a maximum of 14 days prophylaxis treatment in high-risk patients post major surgery.”

2 Abatacept (Orencia) for Rheumatoid Arthritis

- 2.1 The Committee considered an application from Bristol-Myers Squibb for the funding of abatacept (Orencia) for use in combination with methotrexate for treatment of moderate to severe active rheumatoid arthritis in adults who have had an insufficient response to, or are intolerant to, other disease modifying antirheumatic drugs (DMARDs).
- 2.2 The Committee considered that the evidence supplied in the application was of good strength and quality. The Committee noted that the results of Study IM101102 (AIM, reported as Kremer et al. *Ann Int Med* 2006;144:865-76), a randomised, double-blind, placebo-controlled trial conducted in 652 patients with active rheumatoid arthritis despite methotrexate treatment, demonstrated that abatacept plus methotrexate produced significant reductions in disease activity in this patient group compared with methotrexate alone.
- 2.3 The Committee noted that abatacept was not registered for use as monotherapy, and that clinical trials had failed to show a benefit of abatacept monotherapy over placebo.
- 2.4 The Committee noted that abatacept had similar efficacy to infliximab and was better tolerated in Study IM101043 (ATTEST, reported as Schiff et al. *Ann Rheum Dis* 2008;67:1096-1103), which compared abatacept with infliximab and with placebo in addition to background methotrexate in 431 patients with rheumatoid arthritis and an inadequate response to methotrexate.
- 2.5 The Committee noted that the results of Study IM101029 (ATTAIN, reported as Genovese et al. *New Engl J Med* 2005;353:1114-23) suggested that abatacept provided benefit in patients who have had an inadequate response to tumour necrosis factor (TNF) inhibitor treatment, although the benefit was less than that seen in patients who have failed to respond to non-biologic DMARDs.
- 2.6 The Committee noted that the data from the clinical trials indicate that abatacept is associated with an increased risk of serious infections (including tuberculosis) and allergic reactions, but that there is no evidence of demyelination.
- 2.7 The Committee considered that the indirect comparison of abatacept with adalimumab provided in the application was weak and should not be used as definitive evidence that abatacept at a dose of 750 mg per month has a similar effect to adalimumab at a dose of 40 mg per fortnight for the purposes of cost comparisons.

- 2.8 The Committee noted that at the proposed prices there appeared to be no pricing advantage of abatacept over adalimumab, and the cost of infusion services could make abatacept more expensive (although the Committee noted that the supplier indicated it would be willing to negotiate around this). The Committee considered that the cost of blood testing, monitoring and treatment of side effects in patients taking abatacept would be similar to the non-pharmaceutical treatment costs associated with adalimumab therapy.
- 2.9 The Committee considered that in addition to methotrexate, abatacept would be used in combination with prednisone, non-steroidal anti-inflammatory drugs (NSAIDs) and, potentially, other DMARDs in some patients.
- 2.10 The Committee considered that, at least initially until clinicians became experienced with its use, abatacept would likely be used second line after adalimumab. However, over time it could be used ahead of, or replace the use of, adalimumab in some patients. The Committee noted that some patients dislike self-injecting and may prefer an infusion.
- 2.11 The Committee noted that the retention rate of patients on adalimumab in New Zealand is around 80%, which is higher than international retention rates. The Committee considered that some of these patients would be receiving minimal benefit from treatment with adalimumab, and may respond to abatacept.
- 2.12 The Committee considered that the patient numbers in year one could be higher than estimated by the supplier because in addition to the 40–50 or so patients who would switch from adalimumab there would be a pool of ~100 patients who have discontinued adalimumab due to lack of efficacy and who would likely try abatacept.
- 2.13 The Committee considered that availability of funded abatacept would increase the amount of time that patients were on biological DMARDs but, assuming that patients ceased to take these agents once they ceased to derive benefit, this would be associated with increased health gains as there is likely to be a subset of patients who respond to abatacept after failing to respond to adalimumab (and vice versa).
- 2.14 The Committee considered that there was an unmet clinical need for treatments for rheumatoid arthritis for the estimated 30%–50% of patients who do not derive adequate benefit from the adalimumab. The Committee noted, however, that the application was for use following insufficient response to DMARDs, in which case there is less unmet clinical need due to the availability of adalimumab.
- 2.15 The committee noted that abatacept has serious toxicities and that it should not be used by practitioners who do not treat this condition in their scope of practice.
- 2.16 The Committee considered that the only non-hospital facilities that would be equipped to administer abatacept would be private rheumatology clinics. Therefore, the Committee considered that abatacept was, to all intents and purposes, not a community pharmaceutical.
- 2.17 For this reason alone, the Committee **recommended** that the application to list abatacept on the community Pharmaceutical Schedule be declined. However, the Committee **recommended** that there would be a place for abatacept in the hospital setting.

3 Gemcitabine for Macroscopically Resected Pancreatic Cancer

- 3.1 The Committee considered an application from the New Zealand Association of Cancer Specialists to widen access to gemcitabine to allow for its use as adjuvant treatment of macroscopically resected pancreatic cancer. The Committee noted that this is not a registered indication.
- 3.2 The Committee noted that this application had been recently reviewed by the Cancer Treatments Subcommittee, and that the Subcommittee had recommended that the proposal be progressed.
- 3.3 Members considered that the strength and quality of the evidence in the application was moderate.
- 3.4 The Committee noted that the prognosis of patients with resected pancreatic cancer is poor, and that around 85% of patients will relapse within four years of surgery.
- 3.5 The Committee noted the results of the CONKO-001 study published by Oettle et al (JAMA. 2007 Jan 17;297(3):267-77) that compared gemcitabine with observation in patients with resected pancreatic cancer. Members noted that this showed a significant increase in disease-free survival from 6.9 months to 13.4 months ($p < 0.05$).
- 3.6 The Committee noted an abstract presented at the 2008 American Society of Clinical Oncology meeting, which detailed the final results of the CONKO-001 study. Members noted that in a secondary analysis, median overall survival increased from 20.2 months to 22.1 months for patients administered gemcitabine ($p < 0.05$). This was associated with an increase in 5 year overall survival from 9% in the observation arm to 21% in the gemcitabine arm.
- 3.7 The Committee noted that Grade 3 or 4 toxicities were rare in patients administered gemcitabine in the CONKO-001 trial.
- 3.8 The Committee considered that around 60% of patients would relapse within 12 months of adjuvant treatment with gemcitabine.
- 3.9 The Committee **recommended** that the Special Authority restriction applying to gemcitabine be amended to allow for the adjuvant treatment of macroscopically resected pancreatic cancer.
- 3.10 The Committee also **recommended** that the Special Authority restriction applying to metastatic pancreatic cancer be amended to prevent re-treatment with gemcitabine if disease progression occurs within 12 months of adjuvant treatment.
- 3.11 The Committee gave a high priority to these recommendations.
- 3.12 The Decision Criteria relevant to this recommendation are: (i) *The health needs of all eligible people within New Zealand;* (iv) *The clinical benefits and risks of pharmaceuticals;* (vi) *The budgetary impact (in terms of the pharmaceutical budget and*

the Government's overall health budget) of any changes to the Pharmaceutical Schedule, (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.

4 Varenicline (Champix) for Smoking Cessation

- 4.1 The Committee reviewed an application from Pfizer New Zealand Limited for the listing of varenicline (Champix) on the Pharmaceutical Schedule for the treatment of Smoking Cessation.
- 4.2 The Committee noted that it had considered varenicline in April 2007 and February 2008 and that it had recommended deferring a decision pending additional safety and efficacy data.
- 4.3 The Committee noted various sources of information that considered the efficacy and safety of varenicline including; the Aubin et al (Thorax online 2008 doi:10.1136/thx.2007.090647) trial which it had previously considered and which suggested that the incremental effectiveness of varenicline over NRT was less than indirect comparisons indicated; a small study by Stapleton (Addiction 2007; 103:146-154), which reported higher short-term cessation rates with varenicline than NRT although not when compared to combination NRT; an NHS report (April 2007 to March 2008), which noted that varenicline was the most successful pharmacotherapy in helping people quit with 63% of people quitting versus 53% with bupropion, 49% for NRT and 55% for those receiving no pharmacotherapy; information from the first four Product Safety Update Reports (covering the period May 2006 to May 2008), which showed increasing numbers of neuro-psychiatric events including depression, suicidal ideation, anxiety, depression, agitation and hallucination as well as reports of completed suicide; reports published by the Institute for Safe Medication Practice (May 2006 to April 2008; 2008 Quarter 1; 2008 Quarter 2), which showed a high number of adverse event reports in patients using varenicline; regulatory action taken by the FDA (including banning varenicline in patients with specific occupations), NHS and Health Canada as a result of safety concerns; and a review by the BMJ group in the Drug and Therapeutics Bulletin (Vol 46; No 5; May 2008, pp 1113-1116) which concluded that it is premature to regard varenicline as a first line choice, although it could be used following discussion with the patient regarding safety concerns and that treatment should be combined with regular advice and support from healthcare professionals.
- 4.4 The Committee noted that the application showed that varenicline has a worse tolerability profile than NRT with a higher rate of adverse events and subsequent discontinuations. The Committee considered that while nicotine withdrawal can be associated with adverse events it appears increasingly likely that there is an association between varenicline and serious neuro-psychiatric events. The Committee also considered that while some patients experiencing serious neuro-psychiatric events had pre-existing psychiatric disorders, many of these were relatively mild conditions which and would not be expected to present with serious problems such as psychotic symptoms and suicidal behaviour as appears to have been occurring with the use of

varenicline. Furthermore, the Committee noted that there have been many reports in patients with no known pre-existing psychiatric disease.

- 4.5 The Committee considered that the safety signal is real, the number of adverse events is increasing, there are concerns with the safety profile of varenicline, and there is limited evidence that varenicline is more effective than NRT. The Committee further noted that the incremental quit rate of varenicline over NRT is relatively small. However, the Committee also considered that there is a real benefit in stopping smoking and that varenicline may have a risk/benefit advantage in patients who have not responded to other smoking cessation treatments including NRT and nortriptyline.
- 4.6 The Committee considered that varenicline should remain in the Intensive Medicines Monitoring Programme (IMMP) and that the datasheet should be updated to reflect recent safety concerns. The Committee recommended that PHARMAC staff write to Medsafe regarding its comments for the need for IMMP monitoring and datasheet upgrade revision to reflect the new information.
- 4.7 The Committee recommended that access to varenicline should be restricted by Special Authority, with similar restrictions as those used in Australia, as follows:

Varenicline - Initial treatment using the starter pack (box containing 11 tablets 0.5 mg and 14 tablets 1 mg) and the 14 day continuation pack (box containing 28 tablets 1 mg)

1. Commencement of short-term therapy as an aid to achieving abstinence in a patient who has indicated that they are ready to cease smoking;
2. The patient is part of, or about to enrol in, a comprehensive support and counselling smoking cessation programme which includes prescriber or nurse monitoring (details of the program must be specified in the Special Authority application);
3. The patient has failed to quit smoking using other smoking cessation treatments including NRT and nortriptyline;
4. The patient has not used varenicline in the last 12 months;
5. Varenicline is not to be used in combination with other smoking cessation treatments and the patient has agreed to this;
6. The patient is not pregnant;
7. The patient is not under the age of 18 years; and
8. The patient has consented to answer follow-up questions from PHARMAC regarding the effects of their varenicline treatment (contact details must be specified in the Special Authority application).

Varenicline - Completion of treatment course using two packs of the 28 day continuation pack (box containing 56 tablets 1 mg)

1. Completion of short-term therapy as an aid to achieving abstinence in a patient who has been issued with an initial treatment Special Authority for varenicline; and the patient is enrolled in a comprehensive support and counselling smoking cessation programme which includes prescriber or nurse monitoring.

- 4.8 The Committee recommended that if varenicline access is limited as above then it could be listed on the Pharmaceutical Schedule with a medium/high priority.
- 4.9 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; (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 (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.

5 Rosuvastatin (Crestor) as a Third-line Lipid Modifying Agent in High Risk Patients

- 5.1 The Committee reviewed an application from AstraZeneca requesting the listing of rosuvastatin as an alternative third-line treatment option to ezetimibe (following treatment failure with simvastatin and atorvastatin).
- 5.2 The Committee noted that it had most recently considered rosuvastatin in August 2007 when it considered that the 40 mg dose could be listed subject to Special Authority restrictions due to safety concerns, that the 10 mg, 20 mg and 40 mg rosuvastatin doses had the same or similar therapeutic effect as the 40 mg, 80 mg and 80 mg atorvastatin doses, and assigned it a low to medium priority for a small number of patients who may benefit from its use.
- 5.3 The Committee noted that AstraZeneca had commenced a compassionate supply programme and that it had agreed to continue supply indefinitely for any patients who begin this programme. The Committee also noted that AstraZeneca had supplied a list of PTAC members addresses to clinicians in order for them to write directly to PTAC members supporting the application for funding and that it had provided clinicians with a standard letter to sign to be included in the AstraZeneca application. The Committee considered that providing PTAC members addresses and a standard letter to clinicians for lobbying purposes was inappropriate, as submissions should only be based on clinically relevant evidence.
- 5.4 The Committee noted information supplied by the AstraZeneca including; the JUPITER study (Ridker et al. New Engl J Med 2008;359:2195-2207); a number of articles and reviews indicating that on a mg per mg basis rosuvastatin is more potent than atorvastatin in terms of lowering LDL-cholesterol; a study by Glueck et al (Clin Ther. 2006 Jun;28(6):933-42); and a number of studies investigating the effect of rosuvastatin on carotid intima-media thickness, carotid plaque volume and atheroma volume.
- 5.5 The Committee noted that the JUPITER study provided the first outcome data for rosuvastatin but considered that its results were not relevant to the third-line patient group.
- 5.6 The Committee considered that the articles and reviews indicating that on a mg per mg basis rosuvastatin is more potent than atorvastatin, at lowering LDL-cholesterol provided

no new information and that the dose equivalence established at the August 2007 meeting reflect this.

- 5.7 The Committee noted that the study by Glueck (2006) indicated that 50 patients who were unable to tolerate atorvastatin and 23 who were unable to tolerate both simvastatin and atorvastatin could tolerate rosuvastatin. However, the Committee considered that this study was a small (n=61) open-label uncontrolled before-and-after pilot study and that the results would need to be reproduced in a larger more robust study before any conclusion could be made.
- 5.8 The Committee noted studies, including METEOR (Crouse et al. JAMA 2007 297:1344-1353), ORION (Hunter et al American Heart Journal, 2008;155:584.e1-584.e8) and ASTEROID (Nissen et al JAMA 2006;295:1556-65) which investigated the effect of rosuvastatin on carotid intima-media thickness, carotid plaque volume and atheroma volume. The Committee considered that the relevance of these studies was limited as they did not compare rosuvastatin to ezetimibe and noted the Cardiovascular Subcommittee of PTAC, when considering the ENHANCE trial, considered that LDL cholesterol is a more robust marker for cardiovascular disease than carotid artery intima-media thickness and LDL cholesterol should be used until clinical endpoints become available.
- 5.9 The Committee considered that it would be unlikely that rosuvastatin would reduce LDL-cholesterol more than the combination of atorvastatin and ezetimibe. However, given that ezetimibe has been relegated as a second or third line agent based on lack of beneficial and at times adverse hard outcome data, mono-therapy with rosuvastatin may be more beneficial than the combination of atorvastatin and ezetimibe. The Committee acknowledged the lack of clinical trial data to back up this conclusion. The Committee did note that, unlike simvastatin and atorvastatin, rosuvastatin is not metabolised via Cytochrome P450 3A4 and that this is a potential advantage.
- 5.10 The Committee **recommended** that rosuvastatin be **listed** with a medium priority on the Pharmaceutical Schedule as a third-line cholesterol lowering agent.
- 5.11 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;*

6 Enzyme Replacement Therapies for Lysosomal Storage Disorders

- 6.1 The Committee considered a proposal from PHARMAC staff to list agalsidase alpha (Replagal), agalsidase beta (Fabrazyme), laronidase (Aldurazyme), alglucosidase alpha (Myozyme), idursulfase (Elaprase) and galsulfase (Naglazyme) on the Pharmaceutical Schedule for the treatment of lysosomal storage disorders.
- 6.2 The Committee noted a letter from Lysosomal Storage Disorders New Zealand to PHARMAC that supported the funding of enzyme replacement therapies for lysosomal storage disorders on the Pharmaceutical Schedule.

Agalsidase alpha (Replagal) and agalsidase beta (Fabrazyme) for Fabry disease

- 6.3 The Committee noted that agalsidase alpha and agalsidase beta had previously been considered by PTAC in 2004 and 2006. The Committee noted that at the previous review it had concluded that agalsidase alpha and agalsidase beta remove globotriaosylceramide (GB-3) from plasma and end organs, but that questions remained around the reliability of surrogate markers used in the clinical studies for predicting clinical benefit, optimum dosing, optimum dosing protocol, initiation of treatment, rationale for the five-fold greater dose of agalsidase beta as compared to agalsidase alpha, and evidence for long term clinical benefits.
- 6.4 The Committee noted the new key evidence comparing agalsidase alpha and agalsidase beta provided in the form of two trials (Vedder et al. 2007 PLoS One 2(7): e598 and Vedder et al. Genetics and Metabolism 2008 in press). The Committee considered that both enzymes were accepted as being functionally indistinguishable. Members noted that the studies did not measure effects on clinical outcomes, instead relying on surrogate markers and end points which have unclear relevance to health outcomes.
- 6.5 Members noted that the Food and Drug Administration had adopted agalsidase beta after noting that agalsidase alpha dosing at 0.2 mg/kg resulted in antibody formation which increased plasma GL3 levels, reduced creatinine clearance and decreased cardiac mass. Members noted that agalsidase beta dosing at 1 mg/kg resulted in a higher percentage of antibody formation (up to 90% in some trials), but had no effect on creatinine clearance and cardiac mass.
- 6.6 The Committee noted the various studies relating to cardiac, gastrointestinal, neurological, vestibular/auditory and renal functions. The Committee reaffirmed its previous view that there was good evidence to support the effect of agalsidase beta on the clearance of GB-3 from plasma and tissue in all age groups and for different ethnicities.
- 6.7 The Committee however considered that there remained no data on the impact on end organ function and the clinical progression of Fabry disease. The Committee considered that theoretically several years of treatment might be necessary before significant benefits are seen and that this raises the possibility that agalsidase alpha and agalsidase beta might be most beneficial early in the course of the disease. Members considered that treating a patient with established Fabry disease might not be beneficial.

- 6.8 The Committee considered that concerns remained around serious adverse effects, infusion related reactions and antibody formation. Members considered that the higher dose of agalsidase beta may saturate the antibodies and negate any negative effect on efficacy compared to the lower dose of agalsidase alpha.
- 6.9 The Committee noted a 2008 Lancet review (Grabowski 2008 Lancet; 372:1263-1271) of Fabry disease that concluded that more data was needed to document long term treatment outcomes and studies to evaluate the effect of treatment on various aspects of the disease process, different dosing regimes of agalsidase alpha and agalsidase beta, and their comparison at the recommended doses and equivalent doses.
- 6.10 The Committee noted a 2006 UK Health Technology Assessment that included a cost-utility analysis. The Committee noted that the estimated cost per quality-adjusted life year (QALY) was high.
- 6.11 The Committee noted that the Pharmaceutical Benefits Advisory Committee (PBAC) had provided funding for agalsidase beta through its Lifesaving Drugs programme and had issued guidelines for treatment. The Committee noted that Canadian Agency for Drugs and Technologies in Health (CADTH) (2004) did not recommend listing agalsidase alpha and agalsidase beta.
- 6.12 The Committee noted that Community Economic Development Assistance Corporation (CEDAC) had concluded that although agalsidase beta affects certain surrogate markers, its impact on clinically meaningful outcomes has not been proven in randomised trials or in subsequent observational studies.
- 6.13 The Committee considered that the outstanding questions from the last review of agalsidase beta in 2006 remained and were not addressed in this application.

Laronidase (Aldurazyme) for Hurlers disease (MPS 1)

- 6.14 The Committee noted that Aldurazyme was used for the treatment of alpha-L-iduronidase deficiency, which is a progressive multi-system disease affecting respiratory, cardiac, skeletal, ophthalmic, and central nervous system (CNS) functions. Members noted that there were 3 phenotypes (Hurler, Schieie, and Hurler-Schieie).
- 6.15 The Committee noted laronidase was administered as a weekly infusion at a dose of 100U/kg.
- 6.16 The Committee noted the key evidence of efficacy provided in the form of one randomised controlled trial (Wraith et al. Pediatrics 2004;144:581-588), a 3.5 year open label extension to the RCT (Clarke et al. Pediatrics 2009;123:229-240) and an open label, prospective trial in patients under 5 years (Wraith et al. Pediatrics 2007;120:(1).available online. The Committee noted that an initial phase 1 – 2 trial involving 10 patients (Kakkis et al. N Engl J Med 2001;344:182-188) had not been supplied although a 6 year follow up for the 5 remaining patients had been (Sifuentes et al. Molecular Genetics and Metabolism 2007;90:171-180).
- 6.17 The Committee noted that the Wraith et al. 2004 trial was a randomised, double blind and multi-national study involving 45 patients. The Committee considered that the data were limited in statistical strength and in clinical significance and that the changes in

forced vital capacity (FVC) were modest. The Committee considered there were a number of outstanding safety and efficacy questions although it noted that the FDA approved laronidase in 2003 based on this trial albeit because of the lack of alternative treatments for a rare disease with fatal consequences.

- 6.18 The Committee considered from the clinical trials that there was a consistent effect on end points out to three and a half years and possibly 6 years (but in small numbers). Members considered that the long term impact and effect on morbidity and mortality was unknown and that longer-term studies were required.
- 6.19 The Committee considered that there was a consistent inverse relationship between antibody levels and the degree of reduction in urinary glycosaminoglycan (GAG) levels. Members noted that there were no apparent effects on any other end points.
- 6.20 The Committee noted that laronidase is not a curative treatment nor is it effective in neurological disease because it does not cross the blood-brain barrier. The Committee noted that laronidase may not improve organ systems when irreversible changes have developed. Members noted that this result meant that treatment would only be beneficial if initiated as early as possible after diagnosis.
- 6.21 The Committee noted a 2006 UK Health Technology Assessment that with limited data acknowledged some degree of improvement in patients on enzyme replacement therapy but at a significant cost.
- 6.22 The Committee noted that the PBAC had provided funding for laronidase through its Lifesaving Drugs programme only to Hurler-Schieie phenotype and under set inclusion criteria. Members noted that the Scottish Medicines Consortium (SMC) (2004) and the CADTH (2005) did not recommend funding for laronidase because of limited efficacy and it was not cost-effective.

Alglucosidase alpha (Myozyme) for Pompe disease

- 6.23 The Committee noted that alglucosidase alpha was used for the treatment of glycogen-storage disease type II or acid maltase deficiency (Pompe disease) and was a rare, progressive debilitating and often fatal lysosomal storage disorder. Members noted that Pompe disease allows glycogen to accumulate in multiple tissues, especially skeletal, and cardiac muscle, causing motor, respiratory and cardiac dysfunction.
- 6.24 The Committee noted that the age of onset and rate of deterioration vary considerably, but patients with infantile onset Pompe disease experience symptoms within the first year of life and progress rapidly to death.
- 6.25 The Committee noted alglucosidase alpha was administered as a fortnightly infusion at a dose of 20 mg/kg. Members considered that the optimum dose was uncertain and could be as much as 40 mg/kg.
- 6.26 The Committee noted the key evidence of efficacy provided in the form of two phase 2 trials (Klinge et al. *Neuromuscular Disorders* 2005;24:31 and Kishnana et al. *Pediatrics* 2006;149:89-97) and an open label, prospective trial comparing enzyme replacement therapy with historical controls (Krishnani et al. *Neurology* 2007;68:99-109). Members noted that there were no randomised clinical trials available due to the ethical issues in

including a control group given the rapidly fatal nature of infantile-onset Pompe disease. Members considered that the lack of a control group did not affect the analysis of the data.

- 6.27 The Committee noted that early trials with recombinant human GAA improved survival, cardiac and respiratory function, and motor development in severely affected infants (Amalfitano et al. *Genet Med* 2001;3:132-138, and Van der Hout et al *Inherited Metabolic Disease* 2001;24:267-275). Members noted that these trials had not been included and a trial including patients aged 6 months to 3 years (most likely because it had yet to be published).
- 6.28 The Committee considered that alglucosidase alpha may not improve muscle fibre function when excessive changes have already developed. The Committee considered that the symptoms and progression of the disease suggested that the initiation of treatment should occur as early as possible and preferably before 6 months of age. Members noted that there was no data in the application to show that there is an effect on treatment of infants older than 6 months, children and adults.
- 6.29 The Committee considered that the long term impact and effect on morbidity and mortality was unknown and that longer-term studies were required. The Committee noted the data showing significant infusion associated reactions, antibody formation and included one report of anaphylaxis. Members considered that post marketing surveillance data would be required to monitor these safety issues.
- 6.30 The Committee noted a 2008 *Lancet* review (van der Ploeg 2008 *Lancet*; 372:1342-1353) of Pompe's disease that suggested long term follow up data was needed to fully understand the potential of enzyme replacement therapy and to formulate guidelines for treatment.
- 6.31 The Committee noted that the PBAC (2008) had provided funding for alglucosidase alpha through its Lifesaving Drugs programme for infantile onset Pompe disease and had accepted that treatment does not appear to extend lifespan beyond early childhood. The Committee noted that CADTH (2007) recommended listing alglucosidase alpha in infantile onset Pompe disease, as demonstrated by onset of symptoms and confirmed cardiomyopathy within the first year of life and recommended that experts develop monitoring and exit criteria. Members noted that the SMC (2007) did not recommend funding for alglucosidase alpha because of the high cost per QALY.
- 6.32 The Committee noted that alglucosidase alpha was not yet approved by Medsafe.

Idursulfase (Elaprase) for Hunter disease (MPS 2)

- 6.33 The Committee noted that idursulfase was used for the treatment for the deficiency or absence of the lysosomal enzyme iduronate-2-sulfatase (I2S). Members noted that the enzyme cleaves O-link sulphate moieties from the GAGs dermatan sulphate and heparin sulphate causing accumulation of GAGs in lysosomes in nearly all cell types, tissues and organs.
- 6.34 The Committee noted that pathologically, Hunter disease manifests as upper airway obstruction and macroglossia, restrictive pulmonary disease, cardiomyopathy, heart

valve dysplasia, hepatosplenomegaly, skeletal deformities, limitation of joint mobility, severe learning difficulties and progressive neurological decline.

- 6.35 The Committee noted the disease continuum for Hunter disease between two extremes (severe/type A and attenuated/type B). Members noted that death usually occurs in the first or second decade of life for the severe phenotype, but in the attenuated phenotype patients usually survive into early adulthood.
- 6.36 The Committee noted idursulfase was administered as a weekly infusion at a dose of 0.5 mg/kg. Members considered that the optimum dose was uncertain, however, from the trials appears to be 0.5 mg/kg weekly over 3 hours.
- 6.37 The Committee noted that hematopoietic stem cell transplantation (HSCT) was largely ineffective for Hunter disease.
- 6.38 The Committee noted the key evidence of efficacy provided in the form of one initial phase 1 – 2 trial (Muenzer et al. *Molecular Genetics and Metabolism* 2007;90:329-337 and one phase 2 – 3 trial (Muenzer et al. *Genet Med* 2006;465-473). Members also noted two review articles.
- 6.39 The Committee noted that the Muenzer et al. 2007 trial was a randomised, double blind, placebo-controlled trial involving 12 patients. The Committee noted that the primary end point was the change from baseline in urinary excretion of GAGs and a number of secondary end points. The Committee noted that there was a marked decrease in urinary GAGs by 2 weeks amongst all 3 different dosing groups of patients. The Committee noted that there was a significant difference compared to baseline at 24 weeks and 48 weeks. Members noted that there is an open label extension being continued with all patients receiving idursulfase 0.5 mg/kg.
- 6.40 The Committee noted that the Muenzer et al. 2006 trial was a randomised, double-blind, placebo controlled, multicentre, multinational trial involving 96 patients. The Committee noted that the primary end points were percentage predicted FVC and the 6-minute walk test (6MWT). The Committee noted that there was a significant difference in 6MWT results in the weekly infusion group compared to placebo, but no significant difference between the fortnightly dose group and placebo. Members noted that although there was a dose-related trend that there was no significant difference between either dose group versus placebo in percentage predicted FVC. The Committee noted that the urinary GAG levels were significantly lower versus placebo in both dose groups and that the response in the weekly treatment group was significantly greater than the fortnightly group. Members noted that there is on open label extension being continued with all patients.
- 6.41 The Committee considered that there was limited trial data on the efficacy and safety of idursulfase. The Committee considered that from the clinical trials there was a consistent effect on end points out to 1 year and that most improvement occurs in the first 12 – 18 months of treatment, with little effect thereafter. Members noted that idursulfase is not effective in neurological disease because it does not cross the blood-brain barrier.
- 6.42 The Committee noted that there was no data on patients younger than 5 years of age, quality of life, pain and rates of hospitalisation. Members considered that the long term impact and effect on morbidity and mortality was unknown and that longer-term studies

were required. Members noted that infusion associated reactions can be serious and life threatening.

- 6.43 The Committee noted the Hunter Outcome Survey is a global database monitoring Hunter disease and contains long-term safety and efficacy data of enzyme replacement therapy with idursulfase. Members noted that it currently holds data on 216 patients and is held by the pharmaceutical supplier.
- 6.44 The Committee noted that the PBAC (2007) had rejected the application to list idursulfase because of unacceptably high-cost effectiveness however Australia had provided funding for idursulfase through its Lifesaving Drugs programme. Members noted that the SMC (2007) and the CADTH (2007) also did not recommend funding for idursulfase because of cost effectiveness (CADTH also noted the clinical significance of its effects were not established and that it has no effect on CNS disease).

Galsulfase (Naglazyme) for Maroteaux-Lamy Disease (MPS 6)

- 6.45 The Committee noted that galsulfase was used for the treatment of the deficiency of the lysosomal enzyme N-acetylgalactosamine 4-sulphate (ASB). Members noted that the enzyme affects stepwise degradation of the GAG dermatan sulphate resulting in accumulation of GAGs in lysosomes of a wide range of tissues.
- 6.46 The Committee noted that in the severely affected form this causes a chronically progressive disorder involving multiple organs resulting in death in the second decade of life. Members noted that in the attenuated form patients usually survive well into early adulthood.
- 6.47 The Committee noted that the diagnosis was usually made at 6-24 months when children show deceleration of growth, skeletal deformities, coarse facial features and upper airway obstruction. Members noted that clouding of cornea, communicating hydrocephalus, blindness or heart disease may develop.
- 6.48 The Committee noted galsulfase was administered as a fortnightly infusion at a dose of 1 mg/kg.
- 6.49 The Committee noted the key evidence of efficacy provided in the form of three trials; a phase 1 – 2 trial (Harmatz et al. 2004), an open label trial (Harmatz et al. Pediatrics 2005;115:681-689) and a phase 3 randomised controlled trial (Harmatz et al. Pediatrics 2006;148:533-539).
- 6.50 The Committee noted that the Harmatz et al. 2006 trial was a randomised, double blind, placebo-controlled, multinational and multicentre study involving 28 patients. The Committee considered that the patient population had been contaminated by the inclusion of 11 patients that did not fulfil entry criteria. The Committee noted that the primary end point was the 12 minute walk test distance and secondary end points of 3 minute stair climb distance and the change from baseline in urinary excretion of GAGs. The Committee noted that there was a significant improvement in the 12 minute walk test at 24 weeks versus placebo, a non-significant improvement in 3 minute stair climb distance (although the actual number of steps showed a significance versus placebo), and a significant decrease in urinary excretion of GAGs.

- 6.51 The Committee considered that the data did not result in any significant gains in respiratory, cardiac or musculoskeletal function. Members noted that galsulfase was not effective in neurological disease because it does not cross the blood-brain barrier.
- 6.52 The Committee noted that there was no long-term safety and efficacy data. Members considered that the long term impact and effect on morbidity and mortality was unknown and that longer-term studies were required. Members noted that galsulfase would likely be associated with significant infusion associated reactions and antibody formation.
- 6.53 The Committee noted that the PBAC (2007) had rejected the application to list galsulfase however Australia had provided funding for galsulfase through its Lifesaving Drugs programme. The Committee noted that CADTH and SMC had not considered galsulfase.
- 6.54 The Committee noted that galsulfase was not yet approved by Medsafe.

Overview, summary and considerations

- 6.55 The Committee considered that the enzyme replacement therapies under review all showed variable effects on morbidity and no evidence of effect on mortality. Members considered that the treatment approaches were essentially experimental and considered that entry and exit criteria would be very difficult to establish for these diseases.
- 6.56 The Committee noted the lysosomal storage disorders are relatively common at 1:10,000 however each specific deficiency has a much lower incidence, perhaps less than 1:100,000. The Committee noted that most of these disorders are autosomal recessively inherited, however a few are X-linked recessively inherited, such as Fabry disease and Hunter disease (MPS II).
- 6.57 The Committee noted that PHARMAC already provided funding on the Pharmaceutical Schedule for imiglucerase (Cerezyme) for the treatment of Gaucher's disease via a panel subject to funding availability. The Committee considered that the benefits of imiglucerase for type 1 Gaucher disease were far superior to any of the enzyme replacement therapies in this application.
- 6.58 The Committee noted that the current treatments of lysosomal storage disorders focused on supportive treatment or, for some diseases, stem cell transplants are available. The Committee considered that enzyme replacement therapies have limitations. Members considered that in addition to those already mentioned others included a lack of impact on organ damage already present before the start of treatment, poor response in bone and cardiac valve disease, variability in enzyme replacement therapy uptake from blood stream to cells, across cell types, and between patients can potentially render these ineffective, or less effective.
- 6.59 The Committee noted that all enzyme replacement therapies had a significant financial cost and would likely result in high cost per QALY estimates, as evident from copies of international assessments and two PHARMAC Exceptional Circumstances rapid cost-utility analyses that had been provided in the application. Members noted that to fund all treatments for all patients would have a substantial budgetary impact.

- 6.60 The Committee noted that all treatments were dose/weight dependant and indefinite. Members noted that there were multiple other lysosomal storage disorders and emerging enzyme replacement therapy treatments that had not yet been reviewed.
- 6.61 The Committee considered that these treatments for LSD's compared poorly to other pharmaceuticals in terms of clinical evidence, and cost effectiveness and in general could not be recommended under the current framework. However, the Committee considered that there may be specific circumstances in which use of such treatments might compare reasonably well with alternative pharmaceuticals. The Committee **recommended** that such considerations would be better made through the existing Exceptional Circumstances system (including the use of expert advisors/panel if necessary), noting that the financial impact would be in excess of that Committee's delegation therefore requiring a decision by PHARMAC's Board in each case. The Committee did not consider that a general population based listing on the Pharmaceutical Schedule was appropriate. The Committee therefore **recommended** that the proposal for listing of all six enzyme replacement therapies discussed on the Pharmaceutical Schedule be declined.
- 6.62 The Committee considered that these treatments compare poorly to other medicines that are considered for funding on many grounds including the evidence of benefit on surrogate markers, the relevance of those surrogates to real clinical outcomes, the understanding of their place in therapy, the dosing, and the amount of health gain in relation to the price being charged. The Committee considered that the question of whether to provide general funding for such treatments, at significant cost and to the detriment of other funding opportunities, was a societal question that the Committee did not consider its place to answer.

7 Etanercept (Enbrel) for Severe Chronic Plaque Psoriasis

- 7.1 The Committee considered a re-application from Wyeth to list etanercept (Enbrel) on the Pharmaceutical Schedule for the treatment of patients with severe chronic plaque psoriasis.
- 7.2 The Committee noted that the re-application proposed that etanercept would be listed on the Pharmaceutical Schedule subject to a Special Authority whereby treatment is restricted to patients who have failed to demonstrate an adequate response, as demonstrated by a Psoriasis Area and Severity Index (PASI) assessment, to three of the following four treatments, where failure to achieve an adequate response is demonstrated by a PASI score of greater than 15:
- (i) phototherapy (UVB or PUVA) for three treatments per week for at least six weeks; and/or
 - (ii) methotrexate at a dose of at least 10 mg weekly for at least six weeks; and/or
 - (iii) cyclosporin at a dose of at least 2 mg per kg per day for at least six weeks; and/or
 - (iv) acitretin at a dose of at least 0.4 mg per kg per day for at least six weeks.

The Committee noted that the proposed renewal criteria would restrict treatment to patients who demonstrated an adequate response as evidenced by a reduction in their PASI score of 75% (or more); or evidenced by a relapse to 75% of the baseline PASI score from the initial treatment.

- 7.3 The Committee noted that the supplier's proposed Special Authority was similar to its 2006 application and that proposed in July 2008 for adalimumab (Humira) for severe chronic plaque psoriasis. Members noted that in addition to the above criteria the supplier had proposed a dosing regime of 50 mg per week over a 24 week period intermittently (rather than 12 or 16 weeks of continuous treatment).
- 7.4 The Committee noted the key evidence of efficacy provided in the form of three previously reviewed randomised controlled trials (Gottlieb et al. Arch Dermatol 2003;139:1627-1632; Leonardi et al. N Engl J Med 2003;349:2014-2022; Papp et al. British Journal of Dermatology 2005;152:1304-1312) and one new randomised controlled trial (van de Kerkhof et al. British Journal of Dermatology 2008;159:1177-1185). Members noted that the Leonardi et al. 2003 and Papp et al. 2005 trials had now been published. Members noted that the principal clinical response measure used in the key trials was the proportion of patients achieving a PASI 75 response (i.e. at least a 75% reduction in PASI score relative to baseline) at 12 weeks (and 24 weeks in the Gottlieb et al. trial).
- 7.5 The Committee considered that the strength and quality of the evidence from the randomised control trials was good and considered that the trials provided evidence for efficacy. The Committee noted that a pooled analysis suggested approximately 33% of patients would achieve a PASI 75 response at 12 weeks versus a 3% response on placebo and approximately 56% of patients would achieve a PASI 75 response at 24 weeks versus a 5% response on placebo.
- 7.6 The Committee noted that trials used a dosing range of 25 mg once weekly (qw) to 50 mg twice weekly (bw). The Committee noted that a dose of 25 mg bw was equal to 50 mg qw and that a dose of 50 mg bw was better than 25 mg bw (over 46-49% PASI 75 at 12 weeks versus 30-37%). Members noted that the Papp et al. trial showed no loss of effect on dose reduction from 50 mg to 25 mg bw after 12 weeks initial therapy.
- 7.7 The Committee considered that there were significant improvements in quality of life measures and that these were similar among the 12 week trials and the 24 week trial. The Committee noted the open label extension studies that looked at the requirement for re-treatment, which varied from 12 weeks to 2 years. Members considered the results showed patients maintaining their responses as long as they continue to take 50 mg qw.
- 7.8 The Committee noted two further open-label studies (CRYSTEL (study 101764) and EASE) to support the use of etanercept in a flexible intermittent regimen head-to-head against etanercept continuous treatment. Members noted that these studies used physician global assessment as the primary end point and that neither had yet been published. Members noted that there were differences in the patient groups studied but in both trials, patients received an initial regime to induce a response and then discontinued treatment. Members noted that patients were retreated on relapse, with some differences between the trials. Members noted that comparison groups continued maintenance treatment following initial response. The Committee noted that intermittent dosing was inferior to continuous treatment in terms of maintaining the response, but that

intermittent dosing probably provided an acceptable level of control of psoriasis with less use of etanercept and therefore at lower cost.

- 7.9 The Committee noted that the results from the CRYSTEL trial showed that 100 mg weekly was not more efficacious than 25 mg bw at 12 weeks. Members noted that these results were also similar in the EASE trial. Members noted that in the CRYSTEL trial the time to relapse was a mean of 62 days. Members noted that in both trials, relapse was gradual and retreatment with etanercept appeared to be as effective as initial treatment. The Committee considered that the strength and quality of these trials were poor to moderate and that it did not provide an accurate means to predict long-term usage of etanercept that could be used in cost-effectiveness analysis.
- 7.10 The Committee noted that no new safety issues with etanercept were identified in the clinical trials. The Committee noted that etanercept was associated with an increased risk of serious infection.
- 7.11 The Committee considered that some patients may use etanercept intermittently as a result of clearance (or remission) in psoriasis; however, demand may emerge by patients on first sign of deterioration. The Committee considered that the majority of patients would require ongoing treatment.
- 7.12 The Committee considered that the supplier's patient estimates were probably conservative; however, Australian uptake was slow and it considered that the lack of familiarity with biological agents by dermatologists was likely to contribute to a possible slow uptake in New Zealand.
- 7.13 The Committee reiterated its previous consideration that other biological agents (infliximab, adalimumab, efalizumab, alefacept) were also registered for the treatment of psoriasis and that these treatments are likely to have similar efficacy. The Committee noted however, there are no head to head studies showing superiority of any one agent.
- 7.14 The Committee considered that there was an unmet clinical need for severe chronic plaque psoriasis patients who had failed systemic treatments and that etanercept was an effective treatment for these patients. The Committee considered that there was more and better data for etanercept than when it was last reviewed and **recommended** that etanercept be listed on the Pharmaceutical Schedule with a medium priority. The Committee noted that other biological agents, as above, would be acceptable treatments and that a psoriasis panel with a capped budget could be established to contain expenditure (although probably difficult to manage).
- 7.15 The Committee considered that the renewal criteria should state that photographic evidence demonstrating improvements in psoriasis should be included in the patient's notes, and that this will be randomly audited. The Committee queried why methotrexate was not being given with biological agents to reduce antibody formation as none of the trial reports or publications seemed to address this question.
- 7.16 The Decision Criteria particularly relevant to this recommendation are: *(i) The health needs of all eligible people within New Zealand; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded*

health and disability support services, and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.

8 Palivizumab (Synagis) for the Respiratory Syncytial Virus

- 8.1 The Committee considered a request from a clinician to allow for a pre-approved Hospital Exceptional Circumstances (HEC) system to allow patients at risk of respiratory syncytial virus (RSV) to access palivizumab. The Committee noted that the use of palivizumab for the treatment of RSV was discussed by the Committee in February 2000 (declined), November 2000 (declined) and August 2001 where it was given a moderate priority. Members noted that palivizumab was not currently listed on the Pharmaceutical Schedule following unsuccessful negotiations with the supplier (Abbott Laboratories) and that the application had been subsequently declined by the PHARMAC Board in 2005.
- 8.2 The Committee noted that the application proposed that palivizumab be restricted to infants under 2 years of age with severe chronic lung disease, with supplemental home oxygen requirements (or in the hospital preparing for discharge with the strong expectation of home oxygen).
- 8.3 The Committee noted the key evidence of efficacy provided in the form of a randomised controlled trial (Impact RSV study) and a population based study (Mitchell et al. *Pediatric Pulmonology* 2006;41:1167-1174). Members noted that the principal clinical response measure used in the key trials was the number of hospitalisations with confirmed RSV infection. The Committee considered that the strength and quality of the evidence was poor; however, the Committee noted that further information had been sourced by Committee members (Feldes et al *Eur J Clin Microbiol Infect Dis* 2003;22:774–5) and a system review and economic evaluation by Wang et al (*Health Tech. Assess.*2008;vol 12 No.36).
- 8.4 The Committee considered that the estimated hospitalisation rate for RSV that was provided by the requesting clinician was too high and not supported by clinical data. The Committee considered that the estimated 50% reduction in hospitalisations from treatment with palivizumab was also overstated in the population the requesting clinician was recommending. Members further considered that the expected hospitalisation cost of around \$36,000 was unlikely, the length of stay is generally short and that in very high risk populations the mortality rate from RSV infection still remains low.
- 8.5 The Committee considered that children with chronic lung disease and prematurity do have increased rates of RSV. However, the Committee noted that there had not been significant applications to the HEC panel to justify a need for a pre-approval. Members noted that about half of the applications to HEC had been approved.
- 8.6 The Committee noted a cost-minimisation analysis had been undertaken by PHARMAC staff, which took into account possible savings from reduced hospitalisations. The Committee noted that the cost of palivizumab was likely to be in excess of any potential savings achieved by reduction hospital admission rates. The Committee also noted that a health technology assessment had been undertaken by the University of Birmingham,

which reported a cost per quality-adjusted life year (QALY) range from £63,800-£454,100 (NZ\$170,000- NZ\$1,200,000).

- 8.7 The Committee **recommended** that the application be declined due to the lack of strength and quality of the evidence and the poor cost effectiveness.

9 Cyclosporin A for Steroid-Resistant Nephrotic Syndrome

- 9.1 The Committee considered an application from [s9(2)(a) OIA] to widen the Special Authority restriction for cyclosporin A to allow for its use in steroid-resistant nephrotic syndrome.
- 9.2 The Committee considered that the evidence in support of the application was of moderate strength and quality.
- 9.3 Members noted that cyclosporin A is currently subsidised under Special Authority for steroid-dependent nephrotic syndrome.
- 9.4 The Committee noted that for patients with steroid-dependant nephrotic syndrome, treatment options include cyclosporin A and cyclophosphamide.
- 9.5 The Committee noted the difficulty in conducting clinical research in rare diseases of children, and the low likelihood of well-designed research becoming available to show change in major outcomes such as survival and use of renal replacement therapy and transplants.
- 9.6 The Committee noted a paper by Plank et al (Pediatr Nephrol. 2008 Sep;23(9):1483-93.) that indicated a significant advantage for cyclosporin A over cyclophosphamide in the proportion of steroid-resistant patients achieving complete response or partial response after 12 weeks of treatment (9/15 patients treated with cyclosporin A versus 3/17 treated with cyclophosphamide, $p < 0.05$ ITT).
- 9.7 Members noted that the Committee and the Transplant Immunosuppressant Subcommittee had previously recommended removal of the Special Authority restriction, but that this may not occur in the near future.
- 9.8 The Committee **recommended** that the Special Authority criteria for cyclosporin A be amended to allow for the treatment of steroid resistant nephrotic syndrome. The Committee gave this recommendation a high priority.
- 9.9 The Decision Criteria relevant to this recommendation are: (i) *The health needs of all eligible people within New Zealand;* (iv) *The clinical benefits and risks of pharmaceuticals;* (vi) *The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule,* (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.

10 Bimatoprost and timolol Combination Eye Drops for Glaucoma (Ganfort)

- 10.1 The Committee reviewed an application from Allergan Australia Pty Ltd for the listing of combination bimatoprost 0.03% and timolol maleate 0.5% (Ganfort) eye drops on the Pharmaceutical Schedule for the treatment of open angle glaucoma and ocular hypertension.
- 10.2 The Committee noted the Homer et al, (Arch Ophthalmol 2006; 124: 1553–1557) trial which compared a combination bimatoprost and timolol maleate product to the concurrent use of the individual components. The Committee noted that this trial showed that there was no difference in intra-ocular pressures between the combined and concurrent treatments indicating non-inferiority of the combination product over its individual components in reducing intra-ocular pressure.
- 10.3 The Committee considered that the bimatoprost and timolol maleate combination product has a similar clinical effect to the combination use of the individual products (bimatoprost and timolol maleate).
- 10.4 The Committee considered that if the bimatoprost and timolol maleate combination product was listed on the Pharmaceutical Schedule then it would replace the use of the individual products in new patients.
- 10.5 The Committee considered that there was no clinical reason not to fund the product, and further **recommended** that bimatoprost and timolol maleate combination eye drops only be listed on the Pharmaceutical Schedule if cost-neutral to the Pharmaceutical Schedule. The Committee considered that in determining cost-neutral status, the availability of generic prostaglandin analogues should be taken into account.
- 10.6 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; (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 Travoprost and timolol Combination Eye Drops for Glaucoma (Duotrav)

- 11.1 The Committee reviewed an application from Alcon for the listing of combination travoprost 0.004% and timolol maleate 0.5% (Duotrav) eye drops on the Pharmaceutical Schedule for the treatment of open angle glaucoma and ocular hypertension.
- 11.2 The Committee noted two randomised controlled trials, studies C-02-41 and C-01-70 which compared the combination travoprost and timolol maleate eye drops to the use of the individual components. The Committee also noted a combined analysis of these two trials.
- 11.3 The Committee noted that at 3 month follow-up, patients using the combination treatment product had slightly higher intra-ocular pressure at two of the three measurement times in trial C-02-41, and slightly higher intra-ocular pressure at one of the three measurement times in trial C-01-70. The Committee noted that the combined analysis indicated that the combination treatment had a slightly higher intra-ocular pressure than the two individual treatments used concurrently but that there was no statistical significant difference.
- 11.4 The Committee considered that these studies indicate that intra-ocular pressure is not lowered to the same extent by using a travoprost and timolol maleate combination product compared to the use of the individual products, however the Committee considered that it is unlikely that the difference is clinically significant and therefore considered that combination travoprost and timolol maleate product has a similar clinical effect to the combined use of separate travoprost and timolol maleate eye drop bottles.
- 11.5 The Committee considered that if the travoprost and timolol maleate combination product was listed on the Pharmaceutical Schedule then it would replace the use of the individual products in new patients.
- 11.6 The Committee considered that there was no clinical reason not to fund the product, and further **recommended** that travoprost and timolol maleate combination eye drops only be listed on the Pharmaceutical Schedule if cost-neutral to the Pharmaceutical Schedule. The Committee considered that in determining cost-neutral status, the availability of generic prostaglandin analogues should be taken into account.
- 11.7 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; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

12 Deferiprone (Ferriprox) for Iron Overload

- 12.1 The Committee reviewed an application from Orphan Australia for the listing of deferiprone (Ferriprox) on the Pharmaceutical Schedule for the treatment of iron

overload in patients with thalassaemia major who are unable to take desferrioxamine; or in whom desferrioxamine therapy has proven ineffective. The Committee noted that Medsafe approval is pending and that Orphan Australia intends applying for wider indications with the TGA at a future time.

- 12.2 The Committee noted that at its May 2008 meeting, after a brief review of deferiprone, that it requested PHARMAC staff to investigate the possibility of an application being made by the supplier.
- 12.3 The Committee noted that deferiprone is taken orally 3 times daily and that it is available in a tablet and a liquid form. The Committee noted that this is in contrast to desferrioxamine which is a subcutaneous injection administered over 8 to 12 hours, 5 to 7 days per week, and deferasirox which is a once daily tablet.
- 12.4 The Committee noted that there are significant cost differences between deferiprone, desferrioxamine and deferasirox. However, the committee noted that deferiprone was much more expensive than it had hoped.
- 12.5 The Committee noted a large number of trials illustrating the effect of deferiprone and desferrioxamine or investigating the effect of combination therapy. The Committee noted that there are no trials directly comparing deferiprone to deferasirox.
- 12.6 The Committee noted that the development of deferiprone was tainted in controversy as the lead investigator of Trial LA 01 believed deferiprone to be ineffective and possibly harmful by increasing liver fibrosis. However, the Committee noted that the sponsor believed there were numerous protocol violations and that clinical practice guidelines were not adhered to, that the trial was subsequently stopped, the results were re-analysed, and the liver fibrosis concerns have not been confirmed in subsequent trials.
- 12.7 The Committee noted a meta analysis by Mamtani and Kulkar (British Journal of Haematology 2008;141:882-890) which found that both desferrioxamine and deferiprone were effective in reducing cardiac iron content and that there was no statistically significant difference between them (P=0.9504).
- 12.8 The Committee noted a 2007 Cochrane Review by Roberts et al which included 10 trials and 398 patients and concluded that deferiprone could be used in patients with thalassaemia when desferrioxamine is inadequate or contraindicated.
- 12.9 The Committee noted the 2007 Italian Society of Haematology Practice Guideline which included a systematic review of the literature by an expert panel of physicians. The Committee noted that the guideline recommended that; desferrioxamine should be used as the first line agent including children under 6 years of age; while there is not enough evidence to enable one oral iron chelator to be recommended over the other. Deferasirox has a better safety profile; deferiprone should be used if patients are intolerant to deferasirox; and that combined therapy of deferiprone and desferrioxamine could be used in patients who develop severe iron overload or cardiac disorder.
- 12.10 The Committee noted the 2008 United Kingdom Thalassaemia Society Guidelines which recommended; desferrioxamine as the first line agent for children under 5 years of age and deferasirox as a second line treatment; that desferrioxamine was the gold standard for older patients but deferasirox could be an alternative first line treatment for children

over six years; either deferiprone or deferasirox could be used in patient's failing treatment with desferrioxamine; combined therapy using desferrioxamine and deferiprone could be used in patients with high iron stores; patients with high cardiac iron could switch to deferiprone or a combination of deferiprone and desferrioxamine.

- 12.11 The Committee considered that deferiprone is likely to be slightly inferior in efficacy to desferrioxamine, particularly in relation to chelation of liver iron.
- 12.12 The Committee considered that while there has been some controversy over the side-effect profile of deferiprone including concerns regarding liver fibrosis and agranulocytosis, the liver fibrosis concerns have been largely resolved, and deferasirox is a new agent with a growing list of side-effects which are not fully quantified due to its recent development. However, the Committee considered deferasirox has better clinical trial data compared to deferiprone.
- 12.13 The Committee considered that desferrioxamine should be the first-line treatment and that either deferasirox or deferiprone could be a second/third line treatment depending upon cost. The Committee considered that combination desferrioxamine and deferiprone therapy is appropriate for patients with high cardiac iron stores, and that deferasirox was preferred over deferiprone for children under 6 years of age.
- 12.14 The Committee considered that deferiprone could be restricted by Special Authority to patients (children over 6 years of age and adults) with chronic transfusional iron overload due to congenital inherited anaemias where (i) desferrioxamine is not tolerated or is contraindicated, or (ii) deferiprone is to be used in conjunction with desferrioxamine where the patient has significant cardiac iron overload; or clinically manifested cardiac disease due to iron overload; or patients are not chelating adequately with desferrioxamine.
- 12.15 The Committee recommended that deferiprone be listed on the Pharmaceutical Schedule under the above Special Authority with a high priority (depending upon whether deferasirox is listed or not). The Committee reiterated that deferasirox should be the 2nd line treatment for patients below age of 6 years where desferrioxamine is not tolerated or contraindicated.
- 12.16 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.*

13 Requirement for a biopsy in the Gluten Free Foods Special Authority

- 13.1 The Committee reviewed the biopsy requirement in the Gluten Free Special Foods Special Authority for the diagnosis of coeliac disease.
- 13.2 The Committee noted letters from two clinicians requesting that the biopsy requirement for patients to be eligible for the Gluten Free Special Authority is removed based upon the lack of biopsy facilities, significant delays in the patient having a biopsy, risk associated with a biopsy and the accuracy of tissue transglutaminase blood tests. One clinician recommended that gluten-free foods should be available to patients with a strongly positive tissue transglutaminase blood test and the other clinician recommended that they should be available to all patients with a positive tissue transglutaminase blood test.
- 13.3 The Committee noted that the difficulty with relying on tissue transglutaminase blood tests to diagnose coeliac disease was the issue of false positives.
- 13.4 The Committee noted studies by Barker et al (Pediatrics 2005;115:1341-1346) and Hill and Holmes (Aliment Pharmacol & Ther 2008;27:572-7) which examined whether there were levels of tissue transglutaminase antibodies at which false-positive results are minimised or do not occur at all.
- 13.5 The Committee noted that Barker et al (2005) found that only one patient with a test result over 100 U had a negative biopsy outcome. The Committee noted that Hill and Holmes (2008) found that a cut off level of 30U/ml resulted in no negative biopsy outcomes. The Committee noted that these studies used different tissue transglutaminase tests.
- 13.6 The Committee noted the North American Society for Paediatric Gastroenterology, Hepatology and Nutrition 2004 Guideline for the Diagnosis and Treatment of Coeliac Disease in Children, and the AGA Institute Medical Position Statement on the Diagnosis and Management of Coeliac Disease (2006), which still considers that a biopsy remains the Gold Standard and should be used in the diagnosis of coeliac disease.
- 13.7 The Committee considered that an accurate diagnosis is important and that while the screening tests are useful, the tests used, and the prevalence of coeliac disease are not consistent throughout the country making the generalisability of the studies reviewed an issue.
- 13.8 The Committee considered that while the quality of the testing is improving it is not yet of a standard sufficient to remove the requirement for a biopsy.
- 13.9 The Committee recommended that the biopsy requirement remain in the Gluten Free Special Foods Special Authority.

14 Folic Acid for the prevention of Neural Tube Defects

- 14.1 The Committee reviewed an application from the Ministry of Health requesting that the folic acid tablet strength listed on the Pharmaceutical Schedule is changed from 0.8 mg to 0.4 mg to reduce the possibility of women exceeding the recommended folic acid upper limit of 1.0 mg per day (Australian National Health and Medical Research Council and the New Zealand Ministry of Health, 2005) following the introduction of folic acid fortification while maintaining an acceptable protective effect.
- 14.2 The Committee noted that it had previously considered the appropriate strength of folic acid at its February 2008 meeting.
- 14.3 The Committee noted that folic acid is recommended to be taken periconceptually to reduce the risk of neural tube defects including spina bifida.
- 14.4 The Committee noted that the origin of the 1.0 mg per day upper limit level was a recommendation by the Institute of Medicine (1998), that it was based on the risk of masking irreversible neurological manifestations of vitamin B12 deficiency principally in the elderly, that it has a large safety margin (5 times), and that it was set at 1.0 mg per day to raise awareness that not all folic acid levels may be safe. The Committee considered that women would be on a folic acid supplement for a short period of time, and although this could mask the diagnosis of vitamin B12 deficiency, this was very rare and is a treatable condition in women of child-bearing age.
- 14.5 The Committee noted that a number of studies using folic acid doses up to 4 mg per day (including Wald et al, (Lancet 2001;358:2069-73); Czeizel et al, (N Engl J Med 1992;327:1832-5) Berry et al, (N Engl J Med 1999;341:1485-91) had been reported and that these studies had shown a reduction in Neural Tube Defects (NTD) with no evidence of harm.
- 14.6 The Committee noted that it is not aware of any reports of folic acid toxicity or overdose in New Zealand, that the 5mg dose is currently available, and the datasheets indicates that higher doses have not resulted in any adverse events.
- 14.7 The Committee noted a number of studies, reports and reviews including the Food Standards Australia and New Zealand (FSANZ) 2006 Final Assessment Report "Consideration of Mandatory Fortification with Folic Acid", and the 2006 United Kingdom's Scientific Advisory Committee on Nutrition SCAN report. The Committee noted that these reports did not provide any evidence of any harm with daily folic acid doses of 1.0 mg or more. The Committee noted that a review by Johnston (Paediatric research 2008;63:2-8) concluded that there is no evidence that folic acid supplements cause harm.
- 14.8 The Committee noted a study by Daly et al (Lancet 1997;350:1666-9) which showed that the estimated reduction in the risk of a NTD increased from 22%, to 41% to 47% with folic acid supplements of 0.1 mg, 0.2 mg and 0.4 mg per day respectively.
- 14.9 The Committee noted a study by Wald et al (2001) that used a two-stage model based on published evidence to determine the relationship between folic acid intake and the rate/occurrence of NTD. The Committee noted that using a typical Western countries'

background serum folate level of 5 ng/mL, Wald et al (2001) found that the risk reduction of a NTD per 1000 births increased from 36%, to 51% to 85% with daily folic acid intakes of 0.4 mg, 0.75 mg and 5 mg.

- 14.10 The Committee noted the 2007 Canadian Society of Obstetricians and Gynaecologists Pre-conceptional Vitamin/Folic Acid Supplementation Guidelines published in association with the Motherisk Program, which recommended that a 0.4 to 1.0 mg folic acid daily dosing regime in normal patients, a 5 mg regime in high risk patients, and a 5 mg daily dosing regime in patients with poor compliance.
- 14.11 The Committee noted a number of additional relevant issues including compliance, the increasing prevalence of obesity, and the ability for women to avoid consuming fortified products.
- 14.12 The Committee considered that evidence for the folic acid upper limit of 1.0 mg per day is of grade IV, expert opinion, and that when treating medical conditions the consideration of any upper limit is replaced by consideration of the benefit/risk profile for the individual patient.
- 14.13 With regard to points 14.9 and 14.11 above, the majority of the Committee considered that reducing the strength of the folic acid supplement from 0.8 mg to 0.4 mg could potentially increase the risk of a woman having a NTD-affected pregnancy, even in the context of mandatory fortification of bread with folic acid.
- 14.14 The Committee considered that there was no clinical reason to reduce the strength of the folic acid supplement in a patient and that this could not be justified on clinical grounds.
- 14.15 The Committee noted that the applicants considered that reducing the possibility of exceeding the upper limit of folic acid was in accordance with the precautionary principle, which can be defined as follows: "if an action or policy might cause severe or irreversible harm to the public or to the environment in the absence of a scientific consensus that harm would not ensue, the burden of proof falls on those who would advocate taking the action" (Raffensperger C. & J. Tickner (eds.) (1999) Protecting Public Health and the Environment: Implementing the Precautionary Principle. Island Press, Washington, DC). In fact, the Committee considered that the application of the precautionary principle in this case would mean continued use of the 0.8 mg tablet.
- 14.16 The Committee considered that PHARMAC staff could seek the further clinical opinion of paediatricians and obstetricians regarding the appropriate dosing of folic acid during pregnancy.
- 14.17 The Committee considered that clinically there was no evidence of harm for women who are in the early stages of pregnancy or contemplating pregnancy consuming a 0.8 mg folic acid supplement daily, and that the risk of a NTD could increase if a 0.4 mg folic acid supplement is used instead of a 0.8 mg folic acid supplement. However, the Committee noted that if a 0.4 mg tablet was funded it should be up to the individual clinician to decide on whether they wished to prescribe 0.4 mg or 0.8 mg.
- 14.18 The Committee **recommended** that it had no objection to PHARMAC attempting to source a 0.4 mg tablet, which could then be used for both 0.8 and 0.4 mg dosages.