

February 2005 PTAC Meeting

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.”

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Tenofovir disoproxil fumarate (Viread)

The Committee reviewed an application from Gilead Sciences for the listing of tenofovir disoproxil fumarate (Viread) in Section B of the Pharmaceutical Schedule with the same Special Authority criteria as for other antiretrovirals. The Committee noted that the supplier considered tenofovir to be the first in a novel class of antiretroviral agents called “nucleotide analogues” and claimed it to be active against most nucleotide-resistant viruses. However, the Committee considered that it has the same or similar mode of action as a nucleotide reverse transcriptase inhibitor and should not be placed in its own therapeutic subgroup.

The Committee considered that HIV infection has become a chronic disorder and patients are developing complications due to the disease and drugs. Furthermore, adherence to multi-dose treatment has been identified as an issue. New treatments with less side effects and lower dosing frequency are likely to be more attractive to clinicians and patients. The Committee also noted that response rates among New Zealand patients are comparable to that of Australia.

The Committee noted that there was one study in treatment-naïve patients, where the comparator was stavudine. It noted that stavudine is not the most common first-line therapy in New Zealand. The members noted that the company had attempted to justify treatment in this group of patients on the basis of cost-minimisation, assuming a reduction of side effects and a reduction in the use of lipid-lowering drugs. It considered that the data pertained to the Australian market and needed further analysis for New Zealand. It considered that no evidence had been presented to suggest an unmet need in treatment-naïve patients.

The Committee considered that the two pivotal trials for management of treatment-experienced patients provided good efficacy data. The Committee noted that there was no evidence available to support the use of tenofovir as a second-line therapy or with protease inhibitors except for therapy for treatment-experienced patients. It also noted that there are some concerns raised in papers (not supplied) about a high failure rate when compared with efavirenz in treatment naïve patients. These papers were not included in the application.

The Committee **recommended** that tenofovir be listed on the Pharmaceutical Schedule with a moderate priority for use in treatment-experienced patients. The Committee **recommended** that the application for listing on the Pharmaceutical schedule for treatment-naïve patients should be declined.

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, as there are few options for therapy for treatment-experienced patients.*

Atomoxetine (Strattera)

The Committee reviewed an application from Eli Lilly for the listing of atomoxetine (Strattera) in Section B of the Pharmaceutical Schedule for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The Committee noted that the supplier claimed that atomoxetine has a non-stimulant mechanism of action.

The Committee considered that the studies were short-term for what is considered to be a chronic disease. The Committee considered that it was difficult to conclude whether the pharmaceutical would be associated with withdrawal symptoms or not based on such short trials.

The Committee noted that there was only one direct comparative trial against immediate-release methylphenidate, which contained only 44 patients on immediate release methylphenidate. The members considered that, although the studies showed comparable efficacy to methylphenidate, more data and longer-term trial data were required.

The Committee noted an FDA discussion paper that advised that the labeling of atomoxetine was being updated with a warning about the potential for severe liver injury. It also noted that NICE Guidelines are expected in August 2005.

The Committee **recommended** that the application to list atomoxetine on the Pharmaceutical Schedule should be declined at this time but could be reconsidered when more data becomes available.

The Decision Criteria relevant to this recommendation is: *(iii) the availability and suitability of existing medicines, therapeutic medical devices and related products and related things.*

Escitalopram (Lexapro)

The Committee reviewed an application from Lundbeck for the listing of escitalopram (Lexapro) in Section B of the Pharmaceutical Schedule for the treatment of “Severe Depression”. The Committee noted that PTAC had seen two previous applications in 2003 and 2004 for ‘major depression’ and ‘treatment-resistant depression’ respectively, and that these applications had been declined.

The Committee noted that the new information submitted consisted of a meta-analysis of studies comparing escitalopram and citalopram for severe depression, cost-effectiveness comparison of escitalopram vs citalopram in the treatment of severe depression, and some papers on the effect of different medications on the serotonin transport system.

The Committee considered that the clinical studies were well designed and rigorous. It noted that one study was inconclusive as neither escitalopram nor citalopram was statistically significantly better than placebo. Other studies showed that escitalopram and citalopram were superior to placebo but not statistically significantly different from each other. It considered that there were no major safety concerns and escitalopram was well tolerated with similar side effects to other SSRIs. The Committee noted that the meta-analysis consisted of patients with severe depression and the analysis showed that escitalopram performed better in this group than citalopram. However, it considered the doses of citalopram were too low for severe depression at a mean of 26.4mg/day, and that the patients with severe depression may have been under-treated with citalopram. The Committee also noted the patient numbers in the meta-analysis were small.

The Committee reviewed the cost-effectiveness analysis provided by the supplier. It noted that indirect costs were included in the analysis, which are not used in cost-effective analyses by PHARMAC. It also noted that no evidence of cost-effectiveness versus paroxetine or fluoxetine had been provided. The Committee considered that it was an expensive agent which probably provided only marginal, if any, benefit over existing treatments.

The Committee **recommended** that the application to list escitalopram for “severe depression” on the Pharmaceutical Schedule should be declined.

The Decision Criteria relevant to this recommendation is: *(iii) the availability and suitability of existing medicines, therapeutic medical devices and related products and related things.*

Eloxatin (oxaliplatin) - for the treatment of metastatic colorectal cancer

The Committee noted that in combination with fluoropyrimidine-based therapy this treatment appeared to be as effective as irinotecan, and may be less expensive. However, it noted that such savings might not eventuate if the availability of this treatment simply changed the sequence of treatments used. It considered that this issue would require further analysis by PHARMAC. It supported and endorsed the **recommendation** of CaTSOP to list this treatment only if it is cost-neutral or better.

The Decision Criteria most relevant to this recommendation are *(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.*

Iressa (gefitinib) - for the treatment of advanced or metastatic non small cell lung cancer

The Committee agreed with the findings and **recommendations** of CaTSOP. It recommended that this application be declined.

The Decision Criteria most relevant to this recommendation are *(i) The health needs of all eligible people within New Zealand; (iv) The clinical benefits and risks of pharmaceuticals.*

Alimta (pemetrexed disodium) - for the treatment of malignant pleural mesothelioma

The Committee endorsed the view of CaTSOP in respect of this treatment and **recommended** that the application be listed on the Pharmaceutical Schedule with a low priority. The Committee noted that the severity of the disease in patients treated in the published studies was less than that likely to be encountered in the New Zealand setting. It considered that palliative care was of more benefit to such patients than the modest increase in survival of 3 months over existing therapies associated with this treatment.

The Decision Criteria most 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; (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.*

Treatments for Pulmonary Arterial Hypertension (PAH)

Bosentan (Tracleer)

The Committee noted that the PHARMAC Board had considered a paper on the management of PAH at its 15 December 2004 meeting and had directed PHARMAC staff to seek Pharmaceutical Schedule applications.

The Committee noted that bosentan and iloprost are currently funded via the Hospital Exceptional Circumstances (HEC) scheme, as the rarity threshold for Community Exceptional Circumstances (CEC) has been exceeded.

The Committee noted that there is an estimated prevalence of 120-200 patients with PAH in NZ (using UK prevalence data), of whom only 10-25% would be likely to respond to calcium channel blockers.

The Committee noted that bosentan has received provisional registration with Medsafe in December 2004, pending further information from the company.

The Committee noted that apart from the Channick et al. (2001) and Rubin et al. (2002) randomized controlled trials, the only other evidence of note were open-label extension studies by Sitbon et al. (2003) and Roux et al. (2001), which looked at the long term safety and efficacy of bosentan, and an open-label longitudinal study by Barst et al. (2003) which looked at the safety and efficacy of the drug in paediatric patients with PAH.

The Committee considered that bosentan demonstrated subjective and objective improvements, especially in terms of exercise tolerance, haemodynamic parameters and New York Heart Association (NYHA) functional class. It also considered that outcomes were likely to be better in patients with primary PAH than in those with PAH secondary to connective tissue/collagen vascular disease, although this had not been shown statistically. Members considered that bosentan did not demonstrate clear end point advantages over other unlisted treatments such as nebulised iloprost, sildenafil, or sitaxsentan, although they noted that comparative data was limited. The Committee considered that bosentan represented an advance on currently funded treatments on the Pharmaceutical Schedule such as warfarin, diuretics, and calcium channel blockers. The drug also has an advantage in being orally administered.

The Committee considered that there were significant safety concerns regarding bosentan since the drug is associated with such risks as hepatotoxicity, (effects on CYP450), and potential teratogenicity.

The Committee noted that Actelion's cost projections may be underestimated because the company used US prevalence figures of 12.5 cases per million, whereas UK data suggests a prevalence of 30 to 50 cases per million.

The Committee considered that, in the absence of long-term observational studies, head-to-head studies, and studies using treatments in combination (eg. nebulised iloprost and sildenafil) that address efficacy, survival, safety, quality of life and costs, the approach to managing PAH would largely depend on regional experience, funding constraints, administrative regulations, clinical context and patient preference. The Committee noted that limited randomised controlled trial (RCT) data suggest that bosentan, nebulised iloprost and sildenafil have similar effects.

The Committee **recommended** that the option of a PAH treatment panel be pursued by PHARMAC. Based on the evidence so far supplied on bosentan, the Committee considered that the treatment could be funded through such a mechanism. Additionally, iloprost, sildenafil and other developing treatments for

PAH could also be considered via this mechanism. It noted that the panel would need to operate under strict entry and exit criteria and a budgetary cap. The Committee noted that access to funding for PAH treatments, for those in whom it is appropriate, may currently be sought via Hospital Exceptional Circumstances.

On the basis of clinical evidence, the Committee **recommended** the listing of this treatment on the Pharmaceutical Schedule with a low priority, as the Committee was of the opinion that additional evidence on the use of this treatment in PAH, as outlined above, was required.

However, the Committee noted that there is a significant unmet need in these patients due to the severe nature of this disease, and that only a small proportion of patients can be successfully treated using standard treatments. Therefore, the Committee considered a high priority should be given to finding a method of funding treatments for PAH.

The relevant decision criteria 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; (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.*

Iloprost (Ilomedin)

The Committee noted that the PHARMAC Board had considered a paper on the management of PAH at its 15 December 2004 meeting and had directed PHARMAC staff to seek Pharmaceutical Schedule applications.

The Committee noted that bosentan and iloprost are currently funded via the Hospital Exceptional Circumstances (HEC) scheme, as the rarity threshold for Community Exceptional Circumstances (CEC) has been exceeded.

The Committee noted that there is an estimated prevalence of 120-200 patients with PAH in NZ (using UK prevalence data), of whom only 10-25% would be likely to respond to calcium channel blockers.

The Committee noted that only iloprost IV is registered in New Zealand. This means that the use of the IV solution in a nebuliser to deliver iloprost in an inhaled form is an unregistered use.

The Committee considered that the evidence for nebulised iloprost was weak, and was no better or worse than for other treatment options in PAH. However, members considered that seriously ill patients (NYHA class 4) should probably be treated first with IV prostacyclin or nebulised iloprost or maybe sildenafil, as bosentan, beraprost and subcutaneous prostacyclins may not provide a significant clinical response for several weeks.

The Committee noted the Ghofrani et al (2002) study, looking at acute haemodynamic response, showed the combination of nebulised iloprost and sildenafil 50 mg could have synergistic effects.

The Committee considered that iloprost demonstrated subjective and objective improvements, especially in terms of exercise tolerance, haemodynamic parameters, and NYHA functional class. Members considered that nebulised iloprost did not demonstrate clear end point advantages over other unlisted treatments like bosentan, sildenafil, or sitaxsentan, although they noted that comparative data was limited. The Committee considered that iloprost represented an advance on currently funded treatments on the Pharmaceutical Schedule but noted that the frequency of nebulisations (6-9 times a day) may be inconvenient and may affect patient preference for treatment. The Committee also considered that iloprost has a few minor adverse effects but is generally well tolerated.

The Committee noted that Schering has suggested establishing a fund of \$500,000/year for the treatment of PAH, to be managed by a panel of 2-3 experts in the field instead of a listing under Special Authority.

The Committee considered that, in the absence of long-term observational studies, head-to-head studies, and studies using treatments in combination (eg. nebulised iloprost and sildenafil) that address efficacy, survival, safety, quality of life and costs, the approach to managing PAH would largely depend on regional experience, funding constraints, administrative regulations, clinical context and patient preference. The Committee noted that limited randomised controlled trial (RCT) data suggest that bosentan, nebulised iloprost and sildenafil have similar effects.

The Committee **recommended** that the option of a PAH treatment panel be pursued by PHARMAC. Based on the evidence so far supplied on iloprost, the Committee considered that the treatment could be funded through such a mechanism. Additionally, bosentan, sildenafil and other developing treatments for PAH could also be considered via this mechanism. It noted that the panel would need to operate under strict entry and exit criteria and a budgetary cap. The Committee noted that access to funding for PAH treatments, for those in whom it is appropriate, may currently be sought via Hospital Exceptional Circumstances.

On the basis of clinical evidence, the Committee **recommended** the listing of this treatment on the Pharmaceutical Schedule with a low priority, as the Committee was of the opinion that additional evidence on the use of this treatment in PAH, as outlined above, was required.

However, the Committee noted that there is a significant unmet need in these patients due to the severe nature of this disease, and that only a small proportion of patients can be successfully treated using standard treatments. Therefore, the Committee considered a high priority should be given to finding a method of funding treatments for PAH.

The relevant decision criteria 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; (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.*

Brimonidine tartrate 0.2% and timolol maleate 0.5% (Combigan)

The Committee considered the application of Allergan New Zealand Limited regarding the listing of its combination product Combigan on the Pharmaceutical Schedule.

The Committee considered that the trials submitted by the supplier supporting Combigan's use against the concomitant administration of its components was of good quality, although unpublished. The Committee noted that the supplier claimed that the availability of Combigan would result in less use of the currently fully-funded combination product dorzolamide hydrochloride with timolol maleate (Cosopt) and therefore result in savings as it was offering it at a lower price than Cosopt. However, it noted that there were no studies provided comparing Combigan with Cosopt. Instead, Allergan had provided studies comparing the adjunctive use of brimonidine tartrate and timolol maleate with Cosopt. Some members, however, questioned whether Combigan and Cosopt were comparable, with one of the latter's components being a carbonic anhydrase inhibitor (CAI).

Members considered that there was no unmet clinical need that would be filled by subsidising Combigan. It also considered that the ease of administration by having two glaucoma agents in one preparation represented a marginal gain. The Committee noted that Allergan's price offer for Combigan was greater than the cost of the individual agents.

The Committee **recommended** that Combigan only be listed on the Pharmaceutical Schedule if it did not result in an additional cost to the Pharmaceutical budget.

The relevant decision criteria are: *(iii) the availability and suitability of existing medicines, therapeutic medical devices and related products and related things; and (v) the cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*