

November 2005: PTAC minutes for web publishing

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

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

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1. Testosterone Patches (Androderm)

The Committee considered an application by Mayne Pharma to list testosterone patches (Androderm) in Section B of the Pharmaceutical Schedule for the treatment of testosterone deficiency in males. The Committee considered that the evidence supplied was of questionable strength and quality, and noted that there were no comparative trials with oral testosterone preparations. Members noted that the two small trials of 6 and 12 months duration suggested that the pharmacokinetic profile of testosterone patches better mimics the body's circadian rhythm, and that the patches appeared efficacious in regulation of mood and sexual function.

The Committee considered that there was a clinical need for a non-intramuscular testosterone preparation on the Pharmaceutical Schedule. The Committee considered that two 2.5 mg patches would be equivalent to 120 mg – 160 mg oral dose of testosterone undecanoate (Panteston) or a 250 mg dose of an intramuscular testosterone preparation administered every two to three weeks. The Committee considered that a minority, perhaps 10%, of patients may require more than two 2.5 mg patches daily.

The Committee noted that it would be difficult to predict the likely uptake; however, it considered that the initial uptake was likely to be high but that ongoing use might be limited by skin reactions. The Committee noted that there was potential for off-label use of this product, and considered that testosterone patches should be used only for patients with documented testosterone deficiency.

The Committee noted that the use of testosterone patches may reduce nursing costs if it reduced the number of patients who required an intramuscular injection; however these savings were likely to be small.

The Committee **recommended** that testosterone patches be listed on the Pharmaceutical Schedule with a medium priority, but only if cost neutral to the Pharmaceutical Budget when compared with oral preparations.

The decision criteria relevant to this recommendation are *(iii) the availability and suitability of existing medicines, therapeutic medical devices and related products and related things, (iv) the clinical benefits and risks of pharmaceuticals, (vi) the budgetary impact of any changes to the Pharmaceutical Schedule and (vii) the direct cost to health service users.*

2. **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) in patients who have either contraindications to, do not respond to, or cannot tolerate stimulant medications. The Committee noted that PTAC had considered a previous application in February 2005 for ADHD and that this application had been declined.

The Committee noted that atomoxetine has a non-stimulant mechanism of action. The Committee considered that atomoxetine was not a potential drug of abuse; however the Committee considered that the level of abuse with stimulants should be manageable, particularly with the availability of a longer-acting preparation of methylphenidate.

The Committee noted that there was no new evidence comparing atomoxetine with immediate-release methylphenidate, although there were indirect comparisons of similar studies. The committee considered that a meta-analysis of available, double-blind, placebo-controlled studies clearly established that atomoxetine had a significantly greater response and remission rate compared with placebo over a 12 week period. The committee noted that to date the data did not support the use of atomoxetine in the population proposed by the supplier, i.e patients who have contraindications to, do not respond to, or cannot tolerate methylphenidate. However, the committee considered that from a clinical point of view, if one agent is not tolerated, or is contraindicated, it makes sense to use another agent, that has been shown to be effective for that condition.

The Committee noted that atomoxetine was associated with specific safety concerns. However, the committee considered that the issues of greatest concern, suicidality and hepatic toxicity, constituted a small risk and were being adequately monitored by the sponsor. The Committee considered that the once-daily dosing regimen for atomoxetine was an advantage over methylphenidate, but that some patients may be given twice-daily dosing. The Committee considered that data provided on the safety of longer-term exposure were still limited. The Committee reviewed the NICE final appraisal determination for methylphenidate, atomoxetine and dexamphetamine for ADHD. The Committee agreed with the NICE conclusions that methylphenidate, atomoxetine and dexamphetamine were effective in controlling the symptoms of ADHD relative to no treatment, but they were not able to differentiate between the drugs on the grounds of clinical effectiveness. The Committee also agreed with the NICE conclusion that, for the majority of patients there was a choice of more than one appropriate product on clinical grounds, and that the product with the lowest cost (taking into account the cost per dose and number of daily doses) should be prescribed.

The Committee considered that the CUA provided by the supplier had limitations in that it assumed short-term efficacy would be sustained. The Committee agreed that the cost/QALY would be in the region of \$22,000-\$50,000.

The Committee considered that the proposed Special Authority criteria provided by the supplier were too broad. The Committee considered that available literature did not support high risk of substance abuse, motor tics, Tourettes Syndrome or severe anxiety as valid absolute contraindications for stimulants as suggested by the supplier. The Committee recommended that atomoxetine should be listed on the Pharmaceutical Schedule, with Special Authority criteria, as follows:

Special Authority – Retail Pharmacy

Subsidised for :

1. Once daily dosing; and
2. Treatment with a stimulant has resulted in the development of or worsening of a comorbid mood disorder; or
3. Treatment with a stimulant has resulted in the development or worsening of serious adverse reactions or where the combination of stimulant treatment with another agent would pose an unacceptable medical risk.

Or

4. An effective dose of a stimulant has been trialled and has been discontinued because of inadequate clinical response.

Applications for Special Authority to be made by a psychiatrist or paediatrician. Approvals valid for six months

Not to be used in combination with a stimulant.

Renewal by a psychiatrist or paediatrician. Approvals valid for 2 years for patients meeting the following criteria:

The treatment remains appropriate and the patient is benefiting from treatment.

Initial prescriptions to be written by a psychiatrist, paediatrician or paediatric/psychiatric registrars.

The Committee **recommended** that atomoxetine should be funded under these criteria with a low priority.

The Decision Criteria relevant to this recommendation are: *(i) The Health needs of all eligible people within New Zealand, (iii) the availability and suitability of existing medicines, therapeutic medical devices and related products and related things and (iv) The clinical benefits and risks of pharmaceuticals.*

3. Tiotropium (Spriva)

The Committee considered an application from Boehringer Ingelheim for wider access to tiotropium for moderately severe to severe COPD (FEV₁ 40-60%). Members noted that the Committee had considered this proposal previously in May 2005, at which time the Committee had recommended proceeding only if doing so would be cost-neutral.

The Committee noted that the application included three new trials examining tiotropium, but that all three were placebo-controlled, and not in comparison with ipratropium. Members also noted the recent Cochrane review of tiotropium, which included comparisons with placebo, ipratropium and salmeterol. The Committee noted that the Cochrane review accounted for double-publication of trial data and examined publication bias. Members noted that the Cochrane meta-analysis found a number needed to treat (NNT) of 30 for hospitalisations (against placebo, ipratropium and salmeterol) and an NNT of 14 for exacerbations (against placebo and ipratropium). The Committee noted that studies in the meta-analysis were predominantly for GOLD stage IIb (FEV₁ 30-50% of predicted).

Members considered that the major evidence base for tiotropium was still the Vincken (2002) trial, which is not sufficiently powered to detect changes in hospitalizations and exacerbations in patient subgroups, and so was of limited value in assessing cost-effectiveness in comparison with ipratropium.

The Committee reaffirmed its **recommendation** to list tiotropium only if doing so would be cost-neutral.

The relevant decision criteria were (i) *The health needs of all eligible people within New Zealand;* (ii) *The particular health needs of Maori and Pacific peoples;* (iv) *The clinical benefits and risks of pharmaceuticals;* and (vii) *The direct cost to health service users.*

4. **Tamsulosin / finasteride for BPH (Flomax / Proscar)**

Tamsulosin (Flomax)

The Committee considered a letter from a group of urologists supporting the listing of tamsulosin to improve the urinary flow rate in patients with benign prostate hyperplasia who have tried and failed, through lack of effectiveness or adverse effects, other alpha-adrenoceptor blockers.

PTAC had previously considered tamsulosin in 1997 (August and November) and in 2000 (May).

The Committee noted that the efficacy of tamsulosin is comparable to other alpha-adrenoceptor blockers currently funded. They noted that there is no evidence that patients who do not respond to one of the other alpha-adrenoceptor blockers, will respond to tamsulosin. They also noted that tamsulosin has an anti-hypertensive effect but that this is generally less than the other alpha-blockers at equivalent doses.

The urologists claimed that tamsulosin is far superior to doxazosin mesylate and terazosin hydrochloride and that in brachytherapy patients, who have a three to four month window where they are at a high risk of going into retention, using tamsulosin halves the retention rate. The Committee concluded that these claims were not supported by the literature.

The Committee noted that tamsulosin may have a slightly better adverse effect profile at lower doses and that it may be beneficial for a small group of patients. This group might include post-stroke and diabetes patients with postural hypotension. It may also include the elderly, who may be unsuitable for surgery due to multiple co-morbidities.

Given the available evidence and the cost differential, the Committee noted that it might be difficult to restrict tamsulosin to patients who have experienced adverse effects on other alpha-blockers.

The Committee confirmed its previous **recommendation** that tamsulosin be given a moderate priority for listing on the Pharmaceutical Schedule under special authority restrictions. However, they **recommended** that if the company responds with an appropriate proposal then it could be reviewed for a small group of patients with significant postural hypotension on other alpha-blockers.

Finasteride (Proscar)

The Committee considered a letter from a group of urologists supporting the listing of finasteride for patients with benign prostate hyperplasia who have significant and recurrent haematuria.

It was noted that PTAC had considered finasteride in 1993 (August and October) and in 1994 (March and November) and that the application had been declined by the PHARMAC Board on the 23 April 1997.

The Committee noted that there is no evidence for the use of finasteride for haematuria, and that an alternative, cyproterone acetate, is fully funded.

The Committee also noted that the number of patients was unknown and would be difficult to determine.

The Committee concurred with the PHARMAC Board's decision to decline this application in 1997; however, they considered that finasteride would be a useful alternative for those who cannot tolerate alpha-blockers or surgery.

The Committee **requested** that PHARMAC staff investigate whether a generic preparation is currently available and registered in NZ.

The Committee **recommended** that finasteride, at the prices stated, should be declined.

5. Temozolomide (Temodal) – newly diagnosed glioblastoma multiforme

The Committee reviewed an application from Schering-Plough, and reviewed advice received from the Cancer Treatments Subcommittee of PTAC (CaTSoP) in relation to the use of testing of MGMT-promoter status.

The Committee considered that the key study provided by the supplier was by Stupp et al, however an additional study was also available by Athanassiou et al, both published in 2005.

The two studies investigated the use of temozolomide as adjunctive therapy in combination with radiotherapy in patients with newly diagnosed glioblastoma multiforme, however the patient populations differed in the extent of disease progression at randomisation. The patients in the study by Stupp et al had a generally higher performance status (as measured on the WHO scale), than those in the study by Athanassiou et al (measured on the Karnofsky performance scale). The Committee considered that the patient population in this latter study would be more representative of the patients presenting with glioblastoma multiforme in NZ.

The Committee considered that the available evidence demonstrated that some patients obtain a considerable benefit, with an additional 15% of patients surviving at 2 years compared with radiotherapy alone. The median survival benefits in the two studies were 2.5 months, and 5.7 months respectively.

However, the majority of patients would obtain little benefit from treatment with temozolomide. The Committee considered it appropriate to examine targeting of treatment to those patients likely to benefit from treatment with temozolomide. The Committee had previously reviewed a study on the use of MGMT-promoter status as a predictor of response. The Committee noted that its Cancer Treatments Subcommittee considered such a test to be impractical at present. The Committee noted that difficulties in sample collection and processing meant that even in the research setting useful results were obtained in only about one third of patients. The Committee considered that such a criterion should not currently be considered as a basis for funding, but that the research community should further develop the use of this test.

The Committee considered that, from the data provided, patients with higher performance status (Karnofsky score >80, WHO score 0 or 1) obtained significant benefit with temozolomide treatment, tumour resection (rather than biopsy with no resection) was also predictive of a response.

The Committee **recommended** that temozolomide should be listed on the Pharmaceutical Schedule for the adjuvant treatment of newly diagnosed glioblastoma multiforme in combination with radiotherapy. The Committee recommended that subsidy should be targeted to this patient group possibly by means of a Special Authority. The Committee considered that patients should have a good performance status (Karnofsky score >80 or WHO score 0 or 1) at diagnosis, and preferably a resectable or partially resectable tumour. The Committee gave a high priority to this recommendation. The Committee considered that its Cancer Treatments Subcommittee should review any criteria. The Committee considered that a low priority should be given to funding under criteria that included a poor performance score (Karnofsky score <80 or WHO score 2). The Committee recommended that approvals for funding should be restricted to the initial treatment in combination with radiotherapy followed by a maximum of six cycles of temozolomide.

The Committee considered that there would be unlikely to be significant health sector costs associated with any listing other than the additional pharmaceutical costs, although there may be some extra cost from managing adverse effects of temozolomide. The Committee considered that although temozolomide was associated with adverse effects such as neutropoenia, it was reasonably well tolerated for a chemotherapy agent.

The Committee considered that the following of PHARMAC's Decision Criteria were most applicable to its recommendation: *(i) Health needs of New Zealanders, (iii) clinical benefit and risks (vii) the costs to health service users (viii) Government priorities for health funding.*

6. Raloxifene (Evista)

The Committee considered an application by Eli Lilly for the listing of raloxifene on the Pharmaceutical Schedule under the same Special Authority criteria as applied to alendronate (without the indication of glucocorticosteroid-induced osteoporosis). The Committee noted that the Osteoporosis Sub-committee had seen an application for raloxifene in November 2002, and that PTAC had reviewed the minutes in May 2003. The Committee noted that the papers were of sufficient strength and quality, and indicated that for the treatment of osteoporosis, raloxifene produced a similar therapeutic effect to etidronate. The Committee noted that the evidence suggested that raloxifene was associated with a reduction in risk of breast cancer and produced better cardiovascular outcomes against placebo. The Committee noted that raloxifene appeared to have no significant effect on reduction in non-vertebral fracture. The Committee noted that the data contained no trials on male patients, premenopausal patients, or patients previously non-responsive to a bisphosphonate.

The Committee considered that there was a need for a treatment of osteoporosis in patients who could not tolerate an oral bisphosphonate. The Committee noted that patients who were intolerant to bisphosphonates were generally treated with calcium, Vitamin D and calcitriol either alone or in combination. The Committee considered that raloxifene was less efficacious than alendronate in the treatment of osteoporosis, but may be a suitable alternative if raloxifene could be targeted to patients who were genuinely intolerant to bisphosphonates. The Committee noted that calcitriol is now considered inappropriate treatment of osteoporosis in patients with normal kidney function (who should use calciferol), and suggested that there were potential cost savings that could be applied to fund raloxifene.

The Committee **recommended** that the application, as presented by the supplier, for raloxifene to be listed under the same Special Authority criteria as alendronate be declined. It **recommended** that raloxifene should be listed on the Pharmaceutical Schedule with a high priority for patients intolerant of bisphosphonates.

The relevant decision criteria were *(i) the health needs of all eligible people within New Zealand;* *(iii) the availability and suitability of existing medicines, therapeutic medical devices and related products and related things;* *(iv) the clinical benefits and risks of pharmaceuticals;* and *(v) the cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.*

7. Adrenaline Injector (EpiPen)

The Committee considered the application from CSL for the listing of EpiPen adrenaline auto-injectors on the Pharmaceutical Schedule. Members noted that the Committee had considered this product previously.

The Committee considered that the application was of poor quality, and did not include copies of any of the studies that were referenced in the application. Members noted that the application did not provide any new evidence in support of EpiPen, and that all references were from 2002 and earlier.

The Committee noted one study supplied by PHARMAC staff by Song et al (2005) examining the appropriateness of the EpiPen needle length. Members noted that the results of this study indicate that the EpiPen needle may not be sufficiently long enough to provide an intramuscular injection in some patients.

The Committee noted the cost-utility analysis supplied by CSL. Members noted that CSL had assumed in the CUA that only one device would be prescribed to each patient; however, patients frequently have more than one device at a time.

The Committee noted that CSL had presumed an 80% rate of use in anaphylactic episodes, and did not provide a rationale for this figure. Members noted that this was significantly different from the 29% rate of use found by Gold and Sainsbury (2000). Members noted that CSL had referenced the Gold and Sainsbury paper several times throughout its analysis, but omitted to use this statistic in this instance. The Committee considered that the low rate of use found by Gold and Sainsbury is supported by Colver et al (2005). Members also noted that the Colver paper indicated that, from a study of 222 cases of food-allergic reactions, perhaps 6% might have had a more severe reaction if EpiPen was not available.

The Committee noted that CSL had estimated an annual death rate from anaphylaxis of 1 per 8000 patient-years, and noted that this was significantly higher than that estimated by Kemp (2003) of 1 per 2,000,000 patient-years and by Colver (2005) of 1.16 per 10,000,000 patient-years. Members considered that this over-estimation of the mortality rate would have resulted in an over-estimation of the cost-effectiveness of EpiPen.

The Committee **recommended** that, on the basis of no new evidence in support of the proposal, the Committee's previous recommendation to list with a medium priority should stand.