

**August 2004 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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### **Capsaicin (Zostrix HP) cream**

The Committee considered all the literature supporting the use of capsaicin cream in the management of post-herpetic neuralgia and diabetic peripheral neuropathy. It noted that most of the additional evidence provided by the supplier was poor, with some studies having failed to control confounding in their design. Addressing the study by Biesbroeck, et al (1995), the Committee noted that capsaicin cream was just as effective as oral amitriptyline in reducing pain associated with diabetic neuropathy – 76% of patients reported improvement, more than half of whom described their condition as “much better” or “completely gone.”

However, there was some doubt that a 45 g tube of Zostrix HP would be sufficient for one month’s therapy - based on the recommended dosage of a pea-size amount of cream on the affected area four times a day. Some members also raised concern that the initial burning sensation that patients may experience from using the product could reduce compliance.

While the Committee considered that there was some uncertainty regarding the effectiveness of capsaicin cream in the evidence provided, it noted that there were no topical alternatives listed on the Pharmaceutical Schedule for the treatment of post-herpetic neuralgia or diabetic peripheral neuropathy. Furthermore, while the Committee considered that capsaicin cream did not appear to have any additional efficacy benefits over the currently available systemic therapies, e.g. amitriptyline and carbamazepine, the limited data suggested capsaicin cream provided pain relief with fewer side effects. Finally, the Committee noted that treatment with capsaicin cream would cost less than medication such as carbamazepine or gabapentin. Members considered that, although it would be more expensive than amitriptyline, capsaicin cream might be useful in managing diabetic peripheral neuropathy in the elderly and in amitriptyline-intolerant individuals. The Committee considered that uptake was likely to be limited by the side effects of the product, and the impracticality of applying it to large areas (e.g the whole leg with diabetic neuropathy), or to broken skin.

The Committee **recommended** that capsaicin cream be listed on the Pharmaceutical Schedule with a moderate priority. Members also recommended that that the product be restricted to patients with post-herpetic neuralgia or diabetic peripheral neuropathy, as the cost of widening access to include other conditions may be difficult to contain.

The relevant decision criteria to this recommendation are: (ii) the particular health needs of Maori and Pacific peoples, due to the higher prevalence of diabetes in these populations; (iii) the availability and suitability of existing medicines, therapeutic medical devices and related products and related things, as there are no topical alternatives listed on the Pharmaceutical Schedule; and (iv) the clinical benefits and risks of pharmaceuticals, as capsaicin cream appears to have fewer side effects than other available systemic therapies.

## **Insulin glargine (Lantus)**

The Committee reviewed an application from Aventis to list insulin glargine on the Pharmaceutical Schedule.

The Committee reviewed the studies that had been provided in the submission for the use of this product in patients with type I and type II diabetes. Members noted that the trials were predominantly open-label in design due to the difficulty in blinding participants to the clarity difference between isophane insulin and insulin glargine. They considered that the majority of the trials had adequate sample sizes and treatment duration.

The Committee considered that, to represent a significant advance in insulin treatment, evidence of improved control (measured by HbA1c) and reduced hypoglycaemic episodes (particularly severe hypoglycaemia), as well as simplification in treatment schedules, would be required. Members noted that insulin glargine should provide physiological benefits over existing insulin preparations; however, they considered that the evidence demonstrated only a modest improvement in HbA1c and hypoglycaemic episodes.

The Committee considered that insulin glargine would be of most benefit in particular patient groups, including patients with type-I diabetes who have frequent hypoglycaemic episodes with existing insulin preparations.

The Committee reviewed the cost-effectiveness study provided by the supplier and considered that the modelling used was not appropriate for standard clinical practice. The Committee therefore disagreed with some of the assumptions in the analysis and recommended that PHARMAC conduct its own cost-utility analysis.

Members considered that the Diabetes Sub-committee of PTAC should review the application and that the Sub-committee be asked to recommend appropriate targeting criteria.

The Committee **recommended** that insulin glargine be listed on the Pharmaceutical Schedule, but should also be referred to the Diabetes Sub-committee of PTAC. In view of the high price and modest clinical benefit of insulin glargine compared with currently available insulins the Committee gave a low priority to listing. However, members considered that this recommendation might change if the Diabetes Sub-committee could identify an appropriate target population and if there were a satisfactory CUA.

The decision criteria relevant to the assessment of this application include: (i) the health needs of all eligible people within New Zealand, as diabetes is a major health problem in New Zealand; (ii) the particular health needs of Maori and Pacific peoples, due to the higher prevalence of diabetes in these populations; (iii) the availability and suitability of existing medicines, therapeutic medical devices and related products and related things, as current insulin regimes are far from ideal; (iv) the clinical benefits and risks of pharmaceuticals, as insulin glargine has some clinical advantages over currently available insulins; (v) the budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule in view of the high price of insulin glargine; and (viii) the Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere, as diabetes is a priority for health funding.

### **Infliximab (Remicade) – supplier submission and hospital technical assessment**

The Committee considered an application from Schering-Plough for listing infliximab (Remicade) on the Pharmaceutical Schedule for the treatment of severe rheumatoid arthritis (RA). Members noted that infliximab needs to be administered under the supervision of specialist physicians, and that patients need to be monitored for at least one hour post infusion with emergency supportive care available. They therefore did not consider that infliximab should be administered to patients in the community, and that provision of a community subsidy was not appropriate.

The Committee **declined** the application to list infliximab on the Pharmaceutical Schedule. Members considered that the funding of infliximab should be assessed by individual DHBs for patients on an in-patient basis. Members noted that infliximab was already provided in New Zealand by a number of DHB hospitals.

### **Mycophenolate mofetil (CellCept) in heart transplantation**

The Committee considered an application from Roche for the widening of access to mycophenolate mofetil (CellCept) to include first-line use in the prophylaxis of acute organ rejection after heart transplantation. Members noted that the dose of mycophenolate used in heart transplantation is 1.5g twice a day, which is higher than the dose used in renal transplantation, for which the product is already subsidised under Special Authority for a maximum of one year of therapy.

The Committee considered that the evidence of effectiveness was of good quality and noted that the key study showed an absolute reduction in mortality of 5.2% after one year of treatment and that this benefit was maintained for at least three years compared to azathioprine, when given in combination with cyclosporin and corticosteroids. Members noted that the cost of mycophenolate was substantially higher than azathioprine, but that a number of studies indicated that the use of mycophenolate would reduce the dose of cyclosporin which is a cost offset that would need to be considered in a cost-effectiveness analysis. Members were not aware of whether or not this practice would be followed in New Zealand.

The Committee noted that there is some evidence of a reduction in rates of post-transplant malignancy with a relative risk reduction of 0.73 with mycophenolate use, however the incidence is low so the absolute benefit would be small. Members considered that the request for funding mycophenolate should be considered in light of other potential indications such as renal transplantation and noted that this application would also be considered by the Transplant Immunosuppressant Sub-committee of PTAC at its meeting in October 2004, as part of the general review of access to transplant immunosuppressants.

The Committee **recommended** a moderate priority for listing mycophenolate mofetil on the Pharmaceutical Schedule. However members also recommended that PHARMAC staff conduct a cost utility analysis for PTAC's consideration, and noted that its recommendation for listing mycophenolate may change in light of the results of that analysis.

The decision criteria relevant to the assessment of this application include: (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; (vi) the budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule; and (viii) the Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.

## Memantine (Ebixa) for use in Alzheimer's disease

The Committee considered an application from Lundbeck for the listing of memantine (Ebixa) for the treatment of moderately severe to severe Alzheimer's disease. Members noted that memantine is an N-methyl-D-aspartic acid (NDMA) receptor antagonist and that the pharmacological rationale for its use is based on the observation of elevated glutamate levels in people with Alzheimer's disease. They noted that elevated glutamate is associated with cell death, particularly in the cholinergic neural pathways that are associated with cognition.

The Committee noted that the application was supported by one pivotal study, although a number of others were also provided, including studies of memantine/donepezil combination therapy. Members considered that the studies were relatively small, but well designed given the difficulties of conducting research in patients with later stage Alzheimer's disease. They noted the high dropout rate in the studies, but considered that this would be expected in this patient population. They considered that the studies demonstrated improvements in cognitive scores, behavioural measures and reduced carer time. They also noted that the target population is those patients with a Mini-Mental State Examination score (MMSE) of <14, and that in the New Zealand setting most patients with this severity of dementia would be cared for in an institutional setting. They considered that the clinical significance of the effects of memantine were unclear given the severity of dementia, but the reduced time spent caring for the patient may be of significance to carers. Members did not consider that the evidence demonstrated a reduction in the rate of disease progression.

The Committee considered that the effects of memantine would be the same or similar to acetylcholinesterase inhibitors, although the target population is different. Members considered that, if memantine reduced progression to more expensive levels of care (e.g. hospitalisation, institutionalisation), then it may reduce overall health sector costs. However members also noted that institutionalisation represents a shift in the cost of care from family carers to institutions, and that the cost of "informal" care may be similar to institutional care – as argued in some of the papers provided with the supplier's submission (due to the costs of respite and day care costs, in addition to other costs such as carer time).

The Committee did not consider that the data presented could be used to estimate the cost-effectiveness of memantine, and considered that it would be difficult to justify the listing of memantine on cost-effectiveness grounds.

The Committee noted that there are no alternative funded pharmaceuticals for the treatment of moderate or severe Alzheimer's disease, and considered that there is a need for more effective pharmaceutical treatments. Members considered that, although the place of memantine in therapy is unclear for the majority of patients, there may be a subset of patients for whom treatment is appropriate, although it is not possible to establish from the evidence how to identify these patients. Members considered that memantine should not be given further consideration unless the overall strategy for management of Alzheimer's patients was reviewed.

The Committee **recommended** that the application for listing memantine on the Pharmaceutical Schedule be declined.

## Review of listing Oral Impact with DCS status

The Committee considered an application to list Oral Impact on the Discretionary Community Supply (DCS) list. Members had previously considered this application at its April 2004 meeting, however some of the key studies had been omitted and it was recommended that the application be resubmitted with additional supporting literature. They noted that the key studies had since been provided, although many of these originated from a single institution.

The Committee noted that, by making Oral Impact available through the DCS list, DHB hospitals would have the option to administer it to patients prior to major gastrointestinal or head and neck surgery, although they would not have to provide it in cases where it would not be considered cost-effective. The evidence presented showed the clinical and economic benefits of Oral Impact prior to gastrointestinal or head and neck surgery. The Committee noted that the quality and design of the studies was very good.

Members considered that the daily cost of providing this Oral Impact was relatively low, the clinical benefits were evident for these patients, and **recommended** that it should be listed on the DCS list for use in patients five to seven days prior to major gastrointestinal or head and neck surgery. They recommended that targeting should be used to maintain costs and ensure appropriate usage.

The Committee noted that listing Oral Impact on the DCS list did not obligate DHB hospitals to provide it for all patients who met the criteria, and that hospitals would be able to target it to patients prior to undergoing planned surgical events. It was considered that the reduced length of stay (2.4 days) and a reduction in antibiotics should translate into cost savings for DHB hospitals.

The most relevant decision criteria to the Committee's recommendations were (i) the health needs of all eligible people within New Zealand as the health needs of eligible New Zealanders would be better met, (ii) the availability and suitability of existing medicines, therapeutic medical devices and related products and related things - this product would lead to increased health gains compared to comparative products, (iii) the budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule - the recommendation would have no impact on the pharmaceutical budget as it would be a choice made by individual DHBs, (iv) the direct cost to health service users - the direct cost to patients would be nil; and (v) 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 - cancer is a government priority and most people likely to receive this product would be oncology patients.

## **Tiotropium (Spiriva) for use in COPD**

The Committee noted that both PTAC and the Respiratory Sub-committee of PTAC had previously considered tiotropium. Members also noted that they had previously recommended that tiotropium be listed on the Pharmaceutical Schedule for use in COPD with a high priority.

The Committee noted that PHARMAC staff had provided a preliminary cost-utility analysis (CUA) for its consideration and comment. Members noted that PHARMAC's preliminary CUA both evaluated and revised a CUA provided by the supplier (Boehringer Ingelheim) in 2001. They considered that the CUAs were based on reliable and relevant efficacy data, albeit from a single randomised controlled trial (RCT) (Vinken et al, 2002). They noted with the RCT (which compared tiotropium against a high dose of ipratropium) that while there were some concerns about the level of information provided about randomisation and blinding, the design appeared robust and appropriate. Members also noted there had been some concern expressed by the Respiratory Sub-committee of PTAC over the possibility of bias by using pre-dose morning FEV<sub>1</sub> measurements, however the outcome of reduced hospitalisations was considered the most important variable.

The Committee considered that the assumptions used in PHARMAC's revised CUA were reasonable. Members also considered that the most likely scenario would be that of no further divergence after one year (the limit of the RCT data) — which was — alongside revised tiotropium and ipratropium prices, reduction in all-cause hospitalisations (using marginal costs) and Australian Burden of Disease Study (ABDS) quality of life (QoL) scores. Members considered that any other modelling would be extrapolating data beyond the evidence. They considered that costs were appropriately considered in the CUA, and that PHARMAC's quality adjusted life year (QALY) estimation using the area under the curve is likely to reflect a more realistic QALY gain estimation. They noted the effect of the reduced hospitalisation cost offsets on the CUA was comparatively small.

The Committee considered that to estimate total patient numbers eligible under currently proposed Special Authority criteria was difficult, but considered that it should be possible. Members also considered that likely uptake in New Zealand would best be estimated by considering uptake internationally, noting the rapid uptake in Australia. They noted anecdotally that, of the patients who started on tiotropium, around one half continues on it. They also noted that the Van Noord and Vincken studies suggested that more patients ceased using ipratropium than they did tiotropium.

The Committee noted a proposal from Boehringer Ingelheim to widen access by relaxing the Special Authority criteria from the originally-proposed 40% predicted FEV<sub>1</sub> to a newly-proposed 60% predicted FEV<sub>1</sub>. Members considered that patient numbers would be much larger if eligibility according to disease severity was relaxed in this way. They noted there was no RCT evidence to support a benefit with less severe COPD (where in the Vincken and other RCTs, although patients were eligible with predicted FEV<sub>1</sub>s of 60%, mean FEV<sub>1</sub>s of participants were around 40%), and recommended that the Special Authority eligibility criteria remain as originally proposed.

The Committee noted that the originally proposed Special Authority criteria included usual treatment of ipratropium being at a maximum dose of 80 mcg four times daily (q.i.d.). Members noted that the evidence indicates little advantage of 80 mcg q.i.d. over 40 mcg qid, and that the recent changeover from CFC-containing to CFC-free Atrovent, at a maximum strength of now 21 mcg/puff, meant this criterion should be amended to ipratropium bromide at 42 mcg q.i.d.. They also noted the presence of fixed combination ipratropium / salbutamol inhalers, and questioned whether the proposed Special Authority criteria adequately accounted for this.



The Committee re-affirmed its **recommendation** to list tiotropium with a high priority under the originally proposed criteria, with Special Authority criteria to adequately prevent the concurrent use of ipratropium aerosol inhalers (whether alone or in fixed-dose combinations).

The decision criteria most relevant to this recommendation, as previously noted (at the February 2004 PTAC meeting) are: (i) the health needs of all eligible people within New Zealand: the subcommittee noted that there was a large number of patients with COPD in New Zealand who might benefit from the treatment with tiotropium; (ii) the particular health needs of Maori and Pacific peoples: the subcommittee considered that high burden of disease associated with COPD was especially among Maori and Pacific Islanders (iii) the availability and suitability of existing medicines, therapeutic medical devices and related products and related things: the subcommittee considered that the case for this drug was substantially greater than that for the current widespread use of inhaled corticosteroids; (iv) the clinical benefits and risks of pharmaceuticals: the subcommittee considered that the magnitude of benefits associated with tiotropium use in COPD are clinically relevant; the subcommittee considered that tiotropium is associated with very low risk and the only significant adverse effect is that of a dry mouth; the subcommittee considered that tiotropium provides additional health benefits over and above other pharmaceuticals funded by PHARMAC, e.g. short-acting beta agonists and ipratropium; (vi) the budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule: potentially significant budgetary impact; depending on the access criteria the budgetary impact could potentially be greater than forecasted by the supplier in its submission.

## Growth Hormone for Prader-Willi Syndrome patients

The Committee considered a submission from the Prader-Willi Association (NZ) Inc to reassess the access criteria for growth hormone treatment for children and adolescents with Prader-Willi Syndrome. Members noted that Prader-Willi Syndrome (PWS) is characterised by obesity, short stature, eating disorders, sleep apnoea and resulting cardio-respiratory problems, challenging behaviours and low intellectual ability.

The Committee noted that studies suggested that some children with PWS have growth hormone (GH) deficiency but that classical GH deficiency is not a typical feature of PWS. Members noted that the NZ Growth Hormone Committee (NZGHC) considered that, in their experience, fewer than 20% of PWS patients have classic GH deficiency.

The Committee noted that there were several studies included in the submission that had been conducted to determine the efficacy of GH in patients with PWS but that they were small, mostly not blinded randomised controlled trials (RCTs) and generally of a poor quality. However, members considered that RCTs were difficult to conduct in this group of patients. They noted results of good linear growth responses after one year of GH treatment. They also noted that studies showed improved body composition following GH therapy, most noticeably within the first year. Members noted, however, that there are no long-term studies to confirm maintenance of improved body composition and that a major component of obesity in this disorder is likely to be due to over eating. Members also questioned whether body composition would revert to pre-treatment type if the GH treatment were discontinued.

The Committee noted that many problems associated with this disorder are probably related to features of the syndrome on which GH has not been shown to have an impact. Members noted that the evidence for GH use in patients with PWS did not show enough benefit towards quality of life, morbidity (particularly behavioural and cognitive disturbance) or mortality.

The Committee noted that the NZ Growth Hormone Committee (NZGHC) supports use of GH in some children with PWS. Members noted that it is unclear how long a PWS patient should remain on treatment, with the possibility of therapeutic need being life-long. They also noted that there have been some deaths associated with the use of GH but that a causal relationship between GH and death has not been established.

The Committee noted that widening the GH criteria had been considered three times in the last year and that they had declined each submission.

The Committee noted that the dose required (and therefore the associated cost) for effect on body composition was significantly higher than for increasing linear growth. Members noted that, given the lack of clear evidence of improved body composition on PWS patient morbidity (specifically their main problems of behavioural and cognitive difficulties) and mortality, and the increased dose (and associated cost), they would not recommend GH for PWS patients for the body composition indication.

The Committee agreed that patients with PWS and GH deficiency should have access to GH; however that access should be consistent with that for other GH-deficient patients. The Committee **recommended** that this should be made explicit in the criteria and suggested words to the effect: "for use in those patients with PWS with established GH deficiency".