

## November 2003 Meeting of the Pharmacology and Therapeutics Advisory Committee

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“**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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### **Ipratropium bromide (atrovent) CFC-metered dose inhaler**

The Committee considered an application from Boehringer Ingelheim (NZ) Limited for the listing of ipratropium (Atrovent) 21µg metered dose inhaler (MDI) hydrofluoroalkane (HFA) propellant. The Committee noted that the application to list ipratropium 21µg MDI HFA propellant was due to the supplier phasing out the currently listed CFC-containing ipratropium (Atrovent) 20µg and 40µg MDIs and to keep in line with international protocols limiting the use of CFC-containing propellants.

The Committee noted that the supplier had only provided one study in COPD patients, published in Chest in October 2001. However, the Committee noted that it, and the other unpublished reports, provided evidence of bioequivalence between the ipratropium CFC-free and ipratropium CFC-containing MDIs. The Committee noted that the studies also provided evidence that there were no significant differences in adverse effects between the CFC-free and CFC-containing ipratropium MDIs. The Committee noted that the Medsafe datasheet for ipratropium 21µg MDI HFA propellant draws attention to the difference in the taste of the CFC and HFA formulations.

The Committee considered that there was a clinical need to continue to have ipratropium funded on the Pharmaceutical Schedule.

The Committee recommended that ipratropium (Atrovent) 21µg HFA MDI be listed on the Pharmaceutical Schedule in the same therapeutic subgroup as Atrovent CFC-containing is listed. The Committee gave the recommendation to list a moderate priority until Atrovent CFC-containing is discontinued, at which time the priority would become high.

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### **Carboxymethylcellulose sodium ophthalmic solution (TheraTears)**

The Committee considered an application from Corneal Lens Corporation for the listing of carboxymethylcellulose sodium ophthalmic solution (TheraTears) on the Pharmaceutical Schedule.

The Committee noted that TheraTears was already supplied to optometrists and was relatively expensive. The Committee noted that the submission consisted mostly of promotional materials (including a CD) and did not provide much clinical evidence. The Committee considered that potential for overuse with this product was high, as a large proportion of the population could be potential users. The Committee noted that the Exceptional Circumstances Panel is occasionally asked for a preservative-free eye lubricant and considered that there is a group of patients who could potentially benefit from TheraTears. The Committee noted that the submission did not include evidence showing that the duration of action of TheraTears would be any longer than sodium bicarbonate eye drops.

The Committee recommended that at this stage this application be declined. The Committee noted that if the supplier wished to resubmit the application, and provide more clinical evidence, it would be prepared to reconsider.

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### **Etoricoxib (Arcoxia)**

A Committee member noted that he was engaged in clinical trials for this product and comparators in this group of products and for this reason wished to remain neutral in the decision process. The Chair noted that these were already declared conflicts of interest.

The Committee considered an application from Merck Sharp and Dohme (NZ) Ltd (MSD) for the listing of etoricoxib (Arcoxia) on the Pharmaceutical Schedule for the treatment of acute gouty arthritis. The Committee noted that it had considered the cyclooxygenase-2 (Cox-2) inhibitor class of medications previously, and that the listing of these products had recently been declined by the PHARMAC Board. The Committee noted that the treatment of acute gouty arthritis was not a registered indication for other currently available Cox-2 inhibitors, although considered, from anecdotal evidence, that many comparator products were used for this indication 'off-label'.

The Committee noted the prevalence of gout was higher among Maori and Pacific populations and in particular affected Maori men. The Committee considered that there was a need for effective treatments to be available. The Committee noted that there were alternative treatments currently available for acute gouty arthritis on the Pharmaceutical Schedule, including conventional non-steroidal anti-inflammatory drugs (NSAIDs), colchicine and corticosteroids. The Committee considered that these agents were probably as efficacious as etoricoxib in the treatment of acute gout.

The Committee considered that the supplier's submission was based on claims of similar efficacy and increased tolerability compared with indomethacin. The Committee noted that, although etoricoxib appears to demonstrate similar efficacy in terms of pain relief and joint swelling to the comparator, the supplier considered its primary advantage was its increased tolerability. The Committee noted that although there were increased side effects with indomethacin, it appeared from the studies submitted that there was no significant difference in the number of patients stopping treatment due to side effects. The Committee noted that the supplier had presented efficacy data with respect to rheumatoid arthritis and ankylosing spondylitis. The Committee did not consider this comparison to be useful in their consideration of the submission, which was confined to the treatment of acute gouty arthritis.

The Committee noted that the price contained in the application by the supplier was significantly higher than comparator NSAIDs. The Committee also noted that etoricoxib was more expensive than a NSAID co-prescribed with a proton pump inhibitor. The Committee considered that the diagnosis of acute gout was mostly based on clinical interpretation, and it could be difficult to distinguish from other acute musculoskeletal pain, for example a flare in osteoarthritis. It considered that the resulting high level of prescriber discretion could create difficulties restricting etoricoxib prescribing to acute gout and result in increased prescriptions for other indications such as soft tissue pain or other rheumatic conditions. The Committee considered that the supplier would continue to market this product widely, which could potentially increase expenditure beyond the level indicated in the submission.

The Committee considered that the products already listed on the Pharmaceutical Schedule for the treatment of acute gouty arthritis meet the current clinical need. The Committee recommended that the application to list etoricoxib (Arcoxia) on the Pharmaceutical Schedule be declined.

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### Etanercept (Enbrel) for Juvenile Idiopathic Arthritis (JIA): access criteria

The Committee considered comments from Dr Sue Rudge (Paediatric Rheumatologist) and Wyeth (NZ) Ltd on the draft access criteria for etanercept use in JIA that were discussed in PTAC's meeting in August 2003. The Committee recommended that the following Special Authority Criteria be applied to the listing of etanercept for use in JIA:

#### Initial Application

1. Subsidised as an adjunct to methotrexate therapy or monotherapy where use of methotrexate is limited by toxicity or intolerance.
2. Patient is less than 18 years of age at commencement of treatment.
3. Patient has had severe active polyarticular course Juvenile Idiopathic Arthritis (JIA) for 6 months duration or longer.
4. Patient has tried and not responded to an adequate therapeutic trial of at least three months of each of the following regimens:
  - a. Oral or parenteral methotrexate at a dose of 10-20mg/m<sup>2</sup> weekly in combination with oral corticosteroids (prednisone ≥ 0.25 mg/kg);
  - b. Oral or parenteral methotrexate (10-20mg/m<sup>2</sup> weekly) in combination with one other disease-modifying agent.
5. Patient has persistent symptoms of poorly-controlled and active disease:
  - a. A joint count of at least 20 active joints; or
  - b. At least four active joints from the following: wrist, elbow, knee, ankle, shoulder, cervical spine, hip; and
  - c. Physician's global assessment indicating severe disease.
6. The patient or their legal guardian consents to details of their treatment being held on a central registry and has signed a consent form outlining conditions of ongoing treatment.
7. Application by named specialists only.
8. Initial applications are valid for 16 weeks.

#### Reapplications

1. Subsidised as an adjunct to methotrexate therapy or monotherapy where use of methotrexate is limited by toxicity or intolerance.
2. Patient's response to treatment:
  - a. First reapplication following 12 weeks of treatment the patient should have a ≥ 50% decrease in active joint count and an improvement in physician's global assessment from baseline.
  - b. Further reapplications must demonstrate at least a continuing 30% improvement in active joint count and continued improvement in physician's global assessment from baseline.
3. Reapplications by named specialists.
4. Reapplications are valid for 6 months unless patient fails to meet these criteria at any time during treatment.

The Committee supported the following clinicians as appropriate named specialists:

Dr Sue Rudge (Auckland and Hutt/Wellington)

Dr Archie Kerr (Hutt/Wellington)

Dr Peter Jones (Rotorua)

Dr John Highton (Dunedin)

The Committee considered it appropriate that the named specialist make the initial application following examination of the patient, and also make subsequent reapplications. The Committee recommended that there should be an additional named specialist in Auckland and one in Christchurch. The Committee recommended seeking the opinion of Dr Sue Rudge for appropriate recommendations of the two new specialists.

The Committee also recommended that a central registry of patient information be established.

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### **Widening of access to clindamycin and cefuroxime axetil**

The Committee considered a request from the New Zealand Dental Association (NZDA) to allow dentists access to clarithromycin, clindamycin and cefuroxime axetil for the prophylaxis of haematogenous infection of prosthetic joints during dental interventions.

The Committee noted that there was currently provision for dentists to obtain up to 500 mg of clarithromycin and 450 mg of clindamycin on prescription without restriction. The Committee noted that the intention of this restriction was to limit access in the community to prophylaxis only.

The committee noted that the prophylactic use of antibiotics in the prevention of haematogenous infection of prosthetic joints is not universally accepted as a standard of patient care. The Committee considered that current access to clindamycin and clarithromycin would be sufficient for this indication.

The Committee noted that the evidence presented by NZDA was based on the use of cefuroxime axetil in the prevention of bacterial endocarditis, and was not specific to prevention of infection in prosthetic joints during dental interventions. It considered that, given the relative expense of cefuroxime axetil and its place as a reserved treatment, it would not be appropriate to widen access for use in the community at this time.

The Committee also considered an application from GlaxoSmithKline for widened access to cefuroxime axetil. The Committee noted that there was no evidence provided to show any clinical benefit of cefuroxime axetil over existing subsidised prophylactic antibiotics in penicillin allergy. The Committee considered that this application should be referred, with supporting evidence sourced from the supplier, to the Anti-infective Subcommittee of PTAC for further consideration.

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### Lamivudine

The Committee considered an application\* for the inclusion of lamivudine on the Discretionary Community Supply list for an expanded set of indications over and above the current listing in Section B of the Pharmaceutical Schedule.

*Patients with chronic hepatitis B who have evidence of viral replication and either decompensated liver disease or histologically documented active liver inflammation*

The Committee considered that the evidence presented suggested that lamivudine was effective in improving seroconversion and in preventing cirrhosis and fibrosis. The Committee considered this indication to be adequately covered by the Special Authority Criteria currently listed in the community Pharmaceutical Schedule. The Committee considered that the current Special Authority Criteria targeted treatment to those whom it would be most cost effective to treat.

*HIV patients who are infected with, or who are carriers of, the hepatitis B virus (HBV)*

The Committee considered that the named specialists who cared for these patients already had access to lamivudine, and therefore considered that addition to the DCS list for this indication was not necessary.

*Cancer patients who are infected with, or are carriers of, the hepatitis B virus.*

The Committee noted that reactivation of HBV occurs in approximately 20 to 50% of patients receiving chemotherapy and is often associated with poor outcomes. The Committee considered that, although the evidence involved case reports or small observational studies, it appeared that almost all patients receiving lamivudine did well while undergoing chemotherapy. The Committee considered that clear cost effectiveness had not been shown for this indication. The Committee considered that, although DCS listing would be reasonable, the issue would be better handled by amending the Special Authority Criteria for community access on the Pharmaceutical Schedule.

The Committee recommended that it would be appropriate to widen access to lamivudine by including the following indication in the Special Authority Criteria:

Hepatitis B surface antigen positive (HbsAg) patients who are receiving chemotherapy for a malignancy from commencement and up to two months after chemotherapy treatments have been ceased.

*\*Secretary's note: this item was in response to a request from District Health Boards to include the expanded indications on the Discretionary Community Supply list.*

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### Oxcarbazepine

#### *Neuropathic pain*

The Committee considered a request from two clinicians to list oxcarbazepine on the Discretionary Community Supply list for the treatment of neuropathic pain. The committee reviewed papers relating to this indication that were identified by PHARMAC staff in a literature search. The Committee noted three studies involving the use of oxcarbazepine in patients with neuropathic pain, either with trigeminal neuralgia or painful diabetic neuropathy. Oxcarbazepine was considered as effective as carbamazepine in patients with radiculopathy refractory to gabapentin. Two open, uncontrolled studies showed reasonable pain response, although not as good as surgery, for trigeminal neuralgia. The Committee noted that overall doses between 400-1200 mg per day were used, with better effects observed at a higher dose.

The Committee noted that oxcarbazepine is not registered for neuropathic pain in New Zealand. The Committee noted the paucity of data for its use in neuropathic pain, although there are further studies in progress. The Committee recommended that oxcarbazepine should not be listed on the DCS list for neuropathic pain.

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### **Selegiline**

The Committee considered whether selegiline should remain fully-funded on the Pharmaceutical Schedule.

The Committee noted the results of the Parkinson's Disease Research Group study that reported an excess mortality of one death per 54 patients per year who had received selegiline in combination with levodopa compared to those who received levodopa alone. The Committee noted that the mortality increase was observed primarily in the third and fourth years of treatment, and that the patients who died had a higher rate of falls than the surviving patients. The Committee noted that there had been significant published criticism of this study. The Committee also noted a meta-analysis that had been provided and considered that it did not show any effect of selegiline on mortality.

The Committee considered that selegiline does not increase mortality in patients with Parkinson's disease but, importantly, there is no evidence that combined treatment with selegiline and levodopa confers a morbidity or mortality advantage over levodopa alone in patients with early, mild Parkinson's disease. The Committee considered that patients who receive selegiline may experience some worsening of Parkinson's disease symptoms if treatment is withdrawn.

The Committee recommended that selegiline should remain fully funded for patients currently receiving therapy, but that a part-charge could be introduced for new patients.