

November 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.”

Gemcitabine (Gemzar) for use in bladder cancer	2
Rituximab (Mabthera) for salvage therapy in rituximab-naïve patients	3
Taxanes – use in relapsed gynaecological malignancies	4
Pharmion thalidomide (brand change).....	5
Lanreotide acetate (Somatuline Autogel)	6
Azelastine (Eyezep) eye drops.....	7
Adalimumab (Humira).....	8
Etanercept (Enbrel)	9
Methylphenidate (Concerta) for ADHD	10

Gemcitabine (Gemzar) for use in bladder cancer

The Committee reviewed the application provided by the supplier and supporting evidence provided by a clinician. The Committee also reviewed the record of CaTSOP's discussion in relation to this application.

The Committee noted that the key study of gemcitabine for use in advanced bladder cancer was that by von der Maase, although there were a number of phase II studies with response rates to gemcitabine and platinum therapy of 41-72%. The Committee noted that in the von der Maase study, median survival was 13.8 months in the gemcitabine/cisplatin arm and 14.8 months in the methotrexate, vincristine, doxorubicin, cisplatin arm (MVAC), which was not a statistically significant difference. The Committee noted that the main benefit of gemcitabine therapy was the improved tolerability compared with MVAC, particularly reduced grade 4 neutropenia and mucositis. The Committee noted that this improved tolerability was not reflected in improvements in Quality of Life scores as measured in the study. However, weight loss was reduced and performance scores were improved, both of which were considered to be important QoL surrogates in this patient group.

The Committee noted that the improved tolerability translated into more cycles of gemcitabine/cisplatin with an average of 6 versus 4 in the MVAC arm. The Committee considered that the availability of gemcitabine for use in advanced bladder cancer would result in the treatment of more patients.

The Committee **recommended** that gemcitabine should be listed on the Pharmaceutical Schedule for provision in hospitals for patients with advanced bladder cancer, as recommended by CaTSOP. The Committee gave a moderate priority to this recommendation.

Rituximab (Mabthera) for salvage therapy in rituximab-naïve patients

The Committee reviewed an application from a clinician to provide extended access to rituximab for patients in various settings, and considered the record of the CaTSOP meeting at which this application was discussed. The three indications were:

1. Combination therapy with salvage regime following failure of rituximab-CHOP therapy for diffuse large B-cell non-Hodgkins Lymphoma (DLBCL-NHL);
2. In combination with salvage therapy for relapsed DLBCL-NHL following failure of CHOP chemotherapy, where the patient had not previously been exposed to rituximab due to its unavailability;
3. As maintenance therapy following an autologous stem cell transplant for relapsed DLBCL-NHL.

The Committee noted that none of these indications were approved by Medsafe. The Committee noted that the evidence of benefit for all indications was weak with small patient numbers and no evidence of improved survival, and noted that CaTSOP had considered that the first and third indications should not be progressed. The Committee **recommended** that the applications for these two indications for listing in the oncology basket should be declined.

The Committee reviewed CaTSOP's recommendation to include the second indication in the oncology basket with a high priority. The Committee noted that its previous comments regarding the unregistered nature of the indications and lack of data were applicable here, and that CaTSOP had also commented on these issues. The Committee considered the argument for extending treatment with rituximab to patients who had not had the opportunity to receive the product when they were originally treated with CHOP chemotherapy. The Committee noted that there would be many other occasions where a treatment was made available after the time where earlier patients may have benefited.

The Committee formed the view that it would be inappropriate for PTAC to recommend the listing of a product or indication that had not first been approved by Medsafe. The Committee **recommended** that the application for adding this second indication to the oncology basket be declined. The Committee noted that requests for unregistered indications should be considered under exceptional circumstances.

Taxanes – use in relapsed gynaecological malignancies

The Committee reviewed the application from a clinician to widen access to taxanes to include use in relapsed gynaecological malignancies. The Committee also reviewed the record of the CaTSOP meeting in relation to this application.

The Committee noted that the key study (ICON-4) was a large, controlled comparison of paclitaxel plus platinum chemotherapy versus platinum chemotherapy alone. The Committee noted that this type of study is unusual in oncology. The Committee noted that the ICON-4 study demonstrated a 7% absolute reduction in mortality after 2 years of follow-up (57% vs 50%), and that median survival was improved by 5 months. The Committee noted that the incidence of adverse effects, particularly neurological and alopecia, were greater in the paclitaxel arm of the study. The Committee also noted that Global Health Status and fatigue were worse in the paclitaxel arm. The Committee noted that the ICON-4 study enrolled both patients who had been exposed previously to a taxane, and those who had not. The Committee noted that in the subgroup of patients who had been exposed to a taxane the benefit appeared smaller than in the taxane naïve population, and that the benefit in this subgroup was not statistically significant.

The Committee considered that the results of the ICON-4 study show that paclitaxel is of benefit in second-line therapy where there has not been previous taxane exposure, but that the results are less clear where there has been previous taxane exposure. The Committee also noted that there is still some controversy over the appropriate treatment-free interval before receiving second-line treatment (e.g. 6 vs 12 months).

The Committee considered that, given its lack of registration for this indication, access to docetaxel should not be extended. With regard to paclitaxel the Committee **recommended** that access should be widened and gave this recommendation a low priority.

The Committee noted that the access criteria currently included fallopian and primary peritoneal cancers alongside ovarian cancer, but that these should be excluded from this recommendation since they are unregistered indications.

Pharmion thalidomide (brand change)

The Committee reviewed the application and the record of the CaTSOP meeting. The Committee noted that there are no completed phase III studies of thalidomide, and that in the very small uncontrolled studies available the doses have varied from 100-800 mg/day. There are several Phase III studies being conducted. The Committee noted that many studies used myeloma-protein levels as a marker for efficacy and that the risk of thromboembolism is increased in patients receiving thalidomide in a dose-related manner.

The Committee noted that thalidomide was previously provided under Section 29 of the Medicines Act 1981 through Palmerston North Hospital at a relatively low price, but that Pharmion thalidomide had gained registration, which required the establishment of a risk-management programme. The compliance costs of this programme have meant the cost of Pharmion thalidomide has increased substantially since registration. The Committee noted that for most patients with multiple myeloma the risk management programme was of little benefit as reproductive risk reduction was not an issue in many patients of advanced age. The Committee considered that the substantially increased cost of thalidomide was disproportionate to the benefits, but that due to the inclusion of thalidomide in the oncology basket it had now become standard treatment in New Zealand and a number of patients were receiving treatment. The Committee **recommended** that the Pharmion brand of thalidomide should be listed on the Pharmaceutical Schedule with a low priority.

Lanreotide acetate (Somatuline Autogel)

The Committee reviewed an application from New Zealand Medical and Scientific for the listing of lanreotide on Section B of the Pharmaceutical Schedule with the same Special Authority criteria as octreotide. The Committee noted that there are no randomized controlled trials comparing lanreotide Autogel with octreotide LAR; only sequential studies are available. The Committee considered that the main benefit of lanreotide is related to the Autogel formulation of the product and its ease of administration, since with the octreotide product needle blockages can occur. Lanreotide is a preformulated preparation with a small injection volume and requires deep sub-cutaneous rather than intramuscular injection. The Committee noted that dose equivalence may be an issue with this product at the top end as patients on 30mg of octreotide may require more than 120mg of lanreotide for equivalent control. The sponsor claims that 90 mg of lanreotide appears to be equivalent to around 20 mg of octreotide however in one study a large proportion of people ended up taking 120mg of octreotide.

The Committee considered that if listed, lanreotide would be likely to capture a significant market share from octreotide. The Committee considered that lanreotide has the same or similar therapeutic effect as octreotide and could be put in the same therapeutic subgroup with reference pricing applied. The committee requested that PHARMAC staff obtain data from the sponsor about the difference in selectivity of somatostatin receptor binding between octreotide and lanreotide. The Committee felt that if agents had differences in affinity it would be an advantage to the patient as treatment with octreotide is effective in only a proportion of patients with these conditions.

The Committee **recommended** that lanreotide be listed on the Pharmaceutical Schedule only if a cost-neutral (or better) proposal could be reached.

The Committee considered that PHARMAC's Decision Criteria that would be most relevant to this recommendation would be:

- (iii) the availability and suitability of alternatives – the presentation of lanreotide may be better tolerated than that of the alternative, octreotide.
- (viii) Government's priorities for health funding – cancer is a priority area.

Azelastine (Eyezep) eye drops

The Committee considered Douglas Pharmaceutical's application to list azelastine on the Pharmaceutical Schedule. It noted that azelastine is a histamine H₁-antagonist indicated for allergic conjunctivitis with a similar mechanism of action to levocabastine. The Committee noted that the onset of allergic conjunctivitis may be avoided with the use of mast cell stabilisers. Such preventive treatments include lodoxamide trometamol and sodium cromoglycate, which are currently fully funded.

The Committee considered that the efficacy of azelastine is broadly equivalent to that of levocabastine. Members considered that the evidence pertaining to azelastine's additional anti-inflammatory properties was weak. The Committee also noted that although the supplier's submission stated that azelastine is suitable for both acute and preventive treatment, comparative efficacy data between azelastine and sodium cromoglycate (or other mast cell stabilisers) was not provided.

The Committee considered that fully funding azelastine would be useful, given that levocabastine currently carries a manufacturer's surcharge. However, the Committee noted that expenditure or usage may increase if a patient switch from sodium cromoglycate were to occur.

The Committee **recommended** that azelastine eye drops be listed on the Pharmaceutical Schedule with a low to moderate priority but considered that PHARMAC should assess the financial risk associated with its possible listing.

The relevant Decision Criteria to this recommendation are: (iii) the availability and suitability of existing medicines, therapeutic medical devices and related products and related things, as there are currently no fully funded treatments for acute allergic conjunctivitis but a fully funded preventive medication is available; (vi) the budgetary impact of any changes to the Pharmaceutical Schedule, as there is a risk that expenditure would increase if a switch from mast cell stabilisers to azelastine were to occur; and (vii) the direct cost to health service users.

Adalimumab (Humira)

The Committee noted that adalimumab is a human monoclonal antibody to TNF alpha produced by recombinant DNA technology. As such it has less potential to stimulate an immune response than infliximab, with which it shares similar binding characteristics. It was noted that its terminal half-life of 14 days offered an advantage in frequency of administration compared with etanercept, which must be administered twice weekly.

The main therapeutic claims are that inflammatory disease activity would be reduced, reflected in reductions in CRP and ESR and that joint damage, assessed as radiographic progression would be slowed. The Committee noted that the side effects were similar to other TNF-inhibitors, and included an increased risk of reactivating tuberculosis, injection site reactions and major sepsis.

Four clinical trials were presented, all of which were randomised and of good quality. The AMADA trial compared adalimumab in combination with methotrexate to methotrexate alone over 24 weeks. The STAR trial focused on safety aspects of adalimumab over 24 weeks, and was done in combination with other DMARDs. The van der Putte study was a placebo-controlled trial of adalimumab over 6 months. All trials showed consistent effects on disease activity that were comparable to the effects seen with other TNF inhibitors in other trials, although no head-to-head studies have been done. In the Keystone et al study, radiographic endpoints were assessed over 52 weeks. It appeared that patients treated with adalimumab had significantly less radiographic progression compared with placebo.

The Committee noted that the side effect profile and efficacy of adalimumab and etanercept were highly similar, but noted that there were advantages in the administration of adalimumab compared with etanercept due to the pre-filled syringe and the dose frequency. The Committee noted that no long term safety or efficacy data is yet available for TNF inhibitors. The Committee considered that, if adalimumab were made available, careful targeting would be required, as with other TNF inhibitors, to ensure that only those patients with severe disease resistant to currently funded DMARDs could have access.

The Committee **recommended** that adalimumab, or other TNF-inhibitor, be listed on the Pharmaceutical Schedule with a high priority.

The Committee considered that PHARMAC's Decision Criteria that would be most relevant to this recommendation would be:

(iii) the availability and suitability of alternatives – there is no last-line therapy available for patients with rheumatoid arthritis; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, as this is not considered to be a cost-effective treatment; and (vi) the budgetary impact of any changes to the Pharmaceutical Schedule, as there is a risk that expenditure would increase significantly if adalimumab were listed on the Pharmaceutical Schedule.

Etanercept (Enbrel)

The application was for the use of etanercept for ankylosing spondylitis.

The Committee noted that ankylosing spondylitis (AS) can be a serious and disabling disease, and that in addition to enthesitis and ligamentous ossification some patients also have systemic inflammation.

It was noted that standard current therapy would involve physiotherapy, a stretching programme and long-term, high-dose Non-Steroidal Anti-inflammatory Drugs. DMARDs such as methotrexate and sulphasalazine have not been shown to affect disease progression. The main therapeutic claims for etanercept in the submission were a reduction in spinal pain and improved function.

The Committee reviewed the clinical trial data supplied and noted that only one study, (Davis et al) was of a large size, but that the other studies showed consistent results. Overall, the data quality was good.

The Committee noted that the Davis study involved 277 patients over a period of 24 weeks; the ASAS50 response rate was 59% with etanercept and 28% with placebo. The number needed to treat to achieve an ASAS50 was 4. No head-to-head trials of TNF inhibitors in AS have been carried out to date. No unexpected side effects emerged in the trials; tolerability was similar to rheumatoid arthritis in clinical experience. The Committee considered the lack of long-term data meant that there was no evidence of long-term efficacy or tolerability.

The Committee expressed concerns about the subjectivity of the tests used to measure treatment responses in these patients, as they depend largely on self-reported visual analogue scales. Although the Bath Ankylosing Spondylitis Disease Activity Index and the ASAS50 scale are validated to measure response to treatment in clinical trials, the Committee considered that there could be problems in using measures that have a high degree of subjectivity to determine access criteria. Careful work around any access criteria would be required.

The Committee considered that there was a clinical need for a TNF-inhibitor for a small group of severely affected patients.

Access should be targeted at those patients who experience significant pain and disability and in whom the disease cannot be controlled by NSAIDs such as indomethacin. It was estimated that there may be 70 such patients in New Zealand, although fewer patients may actually seek treatment.

The Committee **recommended** listing etanercept for ankylosing spondylitis on the Pharmaceutical Schedule with a low priority but noted that it should reconsider the priority rating once longer-term data becomes available.

The Committee considered that PHARMAC's Decision Criteria that would be most relevant to this recommendation would be:

(iii) the availability and suitability of alternatives – there is no last-line therapy available for patients with Ankylosing spondylitis; and vi) the budgetary impact of any changes to the Pharmaceutical Schedule, as there is a risk that expenditure would increase significantly if etanercept were listed on the Pharmaceutical Schedule for this indication.

Methylphenidate (Concerta) for ADHD

The Committee considered an application from Janssen-Cilag for listing methylphenidate extended release tablets (Concerta) on the Pharmaceutical Schedule for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The Committee reviewed the research that had been provided in the submission and considered it to be of good quality although there were few long-term studies available. The members noted that there was already a slow-release methylphenidate (Ritalin SR) listed on the Pharmaceutical Schedule. The studies provided did not compare Concerta with Ritalin SR. However, the Committee considered that the release profile of Ritalin SR was such that it may not become effective for up to 3 hours after administration and the duration of effect may be as short as 3 hours in some patients. Concerta provides some theoretical advantages in its release profile with a rapid onset of action followed by a 12-hour controlled-release profile that would provide delivery of methylphenidate throughout the day.

The majority of the Committee **recommended** that Concerta be listed on the Pharmaceutical Schedule, with a moderate priority. However, it considered that the Special Authority criteria recommended by the supplier were too broad and that the estimate of patient numbers was very conservative. The Committee noted that if Concerta were to be funded then the Special Authority would need to be revised.

The decision criteria relevant to the assessment of this application include: (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, as current ADHD regimes are far from ideal; (iv) the clinical benefits and risks of pharmaceuticals, as Concerta has some clinical advantages over currently available pharmaceuticals for treatment of ADHD; (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, as mental health is a priority for health funding.