November 2006: 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."

Note that this is not necessarily a complete record of the PTAC meeting; some material may be withheld for reasons such as protection of supplier commercial information that has been supplied in confidence.

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Record of PTAC meeting held 16 & 17 August 2006

PTAC reviewed the record of the PTAC meeting held on 16 & 17 August 2006 and made the following minor amendments:

Levonorgestrel implants (Jadelle) for contraception – paragraph 9.12: insert ", subject to appropriate restrictions." at the end of the paragraph.

Everolimus (Certican) – paragraph 14.7: Replace "…noted that the rates of organ transplantation…" with "…noted that the requirement for organ transplantation…".

PTAC reviewed the record of the PTAC teleconference held on 14 June 2006 and made the following minor amendment:

The calculated mean pharmacokinetic data in the fed study: Replace

	Cmax	AUCt
Methylpenidate (ref)	6.31	47.98
Methylphenidate (test)	6.23	47.05
Mean ratio(%)	99.25	97.85
90% CI	91.17-108.05	91,73-104.38-103.98

with:

	Cmax	AUCt
Methylpenidate (ref)	6.31	47.98
Methylphenidate (test)	6.23	47.05
Mean ratio(%)	99.25	97.85
90% CI	91.17-108.05	91.73-104.38

Entecavir (Baraclude)

The Committee reviewed an application from Bristol-Meyers Squibb for the listing of entecavir (Baraclude) on the Pharmaceutical Schedule for the treatment of chronic HBV infection in treatment-naïve patients and in lamivudine-resistant, treatment-experienced patients.

The Committee noted that New Zealand has a high prevalence (40 – 85,000 people) of chronic hepatitis B Infection (CHB), particularly in Maori, Pacific Island and Asian peoples. In particular, CHB is responsible for approximately 50% of all chronic liver disease in Maori and Pacific Island people compared with 10% in European New Zealanders. Members noted that at diagnosis approximately 50% of patients would be HBeAg-positive.

The Committee considered that the aims of treatment were to achieve sustained suppression of HBV replication and remission of liver disease in order to manage HBV infection as a chronic disease rather than aiming for a cure.

The Committee noted that there are currently three treatments listed on the Pharmaceutical Schedule under Special Authority criteria for treatment of chronic hepatitis B: lamivudine (Zeffix), interferon alpha 2A (Roferon-A) and 2B (Intron-A) and adefovir dipivoxil (Hepsera) for lamivudine-resistant patients. Members noted that viral resistance to lamivudine is recognized as an increasing problem, which led to the funding of adefovir dipivoxil in May 2006.

The Committee noted that the supplier provided data from six studies; three studies comparing entecavir (ETV) with lamivudine (LMV) in treatment-naive patients, two studies comparing ETV with LMV in lamivudine-resistant patients and one study comparing adefovir with LMV in lamivudine-resistant patients.

The Committee noted that the recommended dose of entecavir is 0.5 mg once daily in CHB treatment-naïve patients, or 1.0 mg once daily for lamivudine-resistant patients (patients with evidence of viraemia while on lamivudine or presence of lamivudine resistance (YMDD mutations).

The Committee considered that the evidence in the application was of reasonable strength and quality for treatment-naïve patients; however, members noted that published data for entecavir was limited to 48 weeks and that there was a lack of long-term follow-up with regard to safety, efficacy and resistance. Importantly, the Committee noted that there were no studies comparing entecavir with adefovir in lamivudine-resistant patients and considered that the data provided was not robust. It considered that, in consequence, the validity of the conclusions drawn by the supplier were doubtful.

The Committee considered that the data demonstrated that, at 48 weeks, entecavir was superior to lamivudine in treatment-naïve HBeAg-positive and -negative chronic HBV patients in terms of histological improvement, reduction in viral load and liver function normalisation.

Members considered that long-term clinical data for adefovir in lamivudine-resistant patients, out to four years, demonstrated sustained efficacy, safety and a low incidence of resistance.

The Committee noted that in the treatment-naïve setting viral resistance to entecavir had not been detected; however, the Committee considered that after longer follow-up entecavir resistance would probably develop as has happened with other hepatitis B treatments. Members noted that in lamivudine-resistant patients treated with entecavir, resistance to entecavir developed in 1% of patients at one year and 9% at two years. Therefore the Committee considered that it is appropriate to await longer-term resistance data.

The Committee noted that entecavir was more expensive than lamivudine and comparably priced with adefovir. The committee noted that in the suppliers cost-utility model the estimated cost/QALY of entecavir was $58,423 for HBeAg-postitive patients and $88,951 for HBeAg-negative patients.

The Committee **recommended** that the application be declined because the place in therapy for entecavir was not clear at this time given the lack of long-term follow-up in treatment-naïve patients and the lack of direct comparison showing an advantage over adefovir in treatment-experienced patients.

The Committee **recommended** that its minute be presented to the Anti-Infective Subcommittee and Hepatitis B experts [ ] for comment.

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.*

Accu-Chek Performa Blood Glucose Meter and Blood Glucose Test Strips and Optium Xceed Blood Glucose Test Meter

Optium Xceed Blood Glucose Meter

The Committee considered an application from Medica Pacifica to list its brand of blood glucose meter, Optium Xceed, on the Pharmaceutical Schedule. It noted that if Optium Xceed was listed on the Pharmaceutical Schedule, the incumbent brand Optium would be delisted.

The Committee noted that the Optium brand of blood glucose testing strips that was currently listed on the Pharmaceutical Schedule was compatible with both the Optium and Optium Xceed blood glucose meters.

The Committee noted testing results for the Optium Xceed blood glucose meter from the Clinical Pathology Department of Auckland City Hospital.

The Committee considered that the Average Imprecision of 5.2% was acceptable. The Committee considered that the Average Bias of +19.3% was high but was acceptable relative to other blood glucose testing meters.

The Committee noted that no testing had been conducted below the blood glucose concentration of 3.6 mmol/L and that it was important that accuracy was maintained below this level.

The Committee noted that Optium Xceed had a larger display and was a smaller device than Optium. The Committee considered that Optium Xceed had improved ease of use over Optium.

The Committee did not object to the listing of Optium Xceed on the Pharmaceutical Schedule. The Committee **recommended** that Optium Xceed be referred to a member of the Diabetes Subcommittee of PTAC for consideration.

Accu-Chek Performa Blood Glucose Meter and Accu-Chek Performa Test Strips

The Committee considered an application from Roche Diagnostics to list its brand of blood glucose meter, Accu-Chek Performa and its brand of blood glucose test strips, Accu-Chek Performa Test Strips, on the Pharmaceutical Schedule. It noted that if Accu-Chek Performa Meters and Test Strips were listed on the Pharmaceutical Schedule, the incumbent brands of Accu-Chek Advantage blood glucose test meters and test strips would be delisted.

The Committee noted that Accu-Chek Advantage test strips are not compatible with the Accu-Chek Performa meter.

The Committee noted testing results for the Accu-Chek Performa blood glucose meter from the Clinical Pathology Department of Auckland City Hospital.

The Committee considered that the Average Imprecision of 6.1% was acceptable. The Committee considered that the Average Bias of +18.5% was high but was acceptable relative to other blood glucose testing meters.

The Committee noted that no testing had been conducted below the blood glucose concentration of 3.8 mmol/L and that it was important that accuracy was maintained below this level.

The Committee considered that Accu-Chek Performa test meter was smaller and appeared easier to use than Accu-Chek Advantage.

The Committee noted that the Accu-Chek Performa test strip required a lower volume of blood to perform testing than Accu-Chek Advantage test strip, offering a significant benefit to patients who had difficulty testing.

The Committee did not object to the listing of Accu-Chek Performa on the Pharmaceutical Schedule. The Committee **recommended** that Accu-Chek Performa be referred to a member of the Diabetes Subcommittee of PTAC for consideration.

Additional Comments:

The Committee considered that there should be no additional patient costs (apart from patient co-payments) associated with switching meters and test strips, such as additional software to read blood glucose testing data.

Tamsulosin hydrochloride (Flomaxtra)

The Committee considered an application from CSL in relation to a new extended-release formulation of tamsulosin (Flomaxtra) for the treatment of benign prostatic hyperplasia (BPH). Members noted that the Committee had previously considered proposals in relation to another extended-release formulation of tamsulosin (Flomax).

The Committee noted that there is a need for alternative treatment for BPH in patients who are intolerant of doxazosin or terazosin.

Members noted that the Committee had previously **recommended** listing with a medium priority for the small group of patients who develop significant postural hypotension on alpha blockers or in whom alpha blockers could not be started due to significant postural hypotension.

Members noted that the Flomaxtra brand was a slight change of formulation over the currently supplied Flomax brand and that the two brands were equivalent in efficacy, although there was a slightly lower incidence of adrenoceptor-related events with Flomaxtra.

The Committee considered that there was insufficient evidence to change the recommendation for tamsulosin.

Etanercept (Enbrel) in Chronic Plaque Psoriasis

The Committee considered an application from Wyeth Pharmaceuticals for the use of etanercept under a defined Special Authority criteria in adult patients with chronic plaque psoriasis.

The Committee considered that the application was of good strength and quality.

The Committee noted three key randomised double-blinded placebo-controlled trials CSR0-51139 (n=118), CSR-51821 (n=611) and CSR-51727 (n=503). The Committee noted that all trials displayed a statistically significant benefit of etanercept over placebo in primary outcome measures with a dose of 25 mg twice-weekly.

The Committee noted that the studies showed that the response was improved with increased dosage or longer duration of treatment, and that, in practice, it was likely that patients would be treated for longer or with doses higher than 25 mg twice weekly.

The Committee noted that the trials provided did not specifically investigate the subgroup of patients that would gain access to treatment under the proposed Special Authority criteria.

The Committee noted that the three trials appeared to be of good quality, although only one of them was published. The Committee noted that the trials were of short duration for what is a long-term condition and need for treatment. The Committee also noted that there were no head-to-head trials comparing etanercept with current standard treatments for plaque psoriasis, such as phototherapy and oral retinoid treatment.

The Committee considered that usage of etanercept would be significantly higher than that proposed due to uncertainty about optimal treatment duration and dosing, and the time taken to relapse, beyond the limited doses and durations used in the three clinical trials.

The Committee considered that chronic plaque psoriasis was a particularly difficult disease to treat and could have a significant negative impact on patients' quality of life. Members considered that there was a relatively wide range of funded treatment options currently available to treat chronic plaque psoriasis; however, the Committee noted that the application was for patients who are resistant to current therapies.

The Committee considered that patients would be likely to persevere with standard treatments despite treatment failure and would be likely to continue standard treatments if initiated on etanercept.

The Committee noted that there were a number of other indication priorities for the funding of TNF-alpha drugs.

The Committee noted that PASI score (Psoriasis Area Severity Index) was the proposed method of measuring severity of disease for determining access to etanercept. The Committee noted that PASI scores were difficult to obtain and were not a routine way of measuring disease severity outside of clinical trials. The Committee noted that the PASI instrument had limited clinical validity and the severity of the PASI score would not necessarily correlate to impact of disease on Quality of Life and considered that a more appropriate method of determining access was required.

The Committee considered that there were no additional significant safety concerns with etanercept in chronic plaque psoriasis compared with etanercept in other disease states. The Committee noted that there was a potential safety concern of increased malignancies and infection associated with etanercept treatment and noted that chronic plaque psoriasis sufferers were at increased risk of skin malignancies due to ultra-violet light treatments.

The Committee noted that no cost-utility data had been provided, but noted the suppliers willingness to provide data if required.

The Committee considered a NICE (National Institute of Clinical Excellence) report on etanercept in plaque psoriasis. The Committee noted that the projected cost-utility was approximately £24,000 per QALY, but that the figure was reduced to £14,460 per QALY when treating severely affected patients requiring hospitalisation. The Committee considered that the projected cost-utility ratio was likely to be relatively high compared with other potential investments. However, the Committee noted that the criteria used by NICE were different to the access proposed in the application and that the cost-utility ratio may be improved under the proposed criteria.

The Committee **recommended** that the application be declined at this time, due to the high projected budgetary impact, the risk of substantial growth, the uncertainty over appropriate access criteria and likely high cost-utility ratio.

Fulvestrant (Faslodex)

The Committee reviewed an application from AstraZeneca for listing fulvestrant intramuscular injection in post-menopausal women with locally advanced or metastatic breast cancer, with subsidy restricted to patients who have failed both tamoxifen and aromatase inhibitor therapies. The Committee also noted a supporting letter from a New Zealand oncologist for this indication.

The Committee noted that fulvestrant forms a new class of antioestrogens that lead to downregulation of oestrogen receptor protein. Fulvestrant blocks the trophic actions of oestrogens without having any partial agonist (oestrogen-like) activity.

The Committee noted that the principal evidence of efficacy comes from two similar phase III trials, in which fulvestrant was compared to anastrazole.

The study by Howell et al (Trial 0020) randomised 451 patients to open-label fulvestrant (250mg each month) or anastrazole (1mg daily). Another arm of the study using 125mg fulvestrant per month was terminated due to lack of therapeutic effect. The publication reported a median follow-up of 14.4 months.

The Committee noted that almost 97% of patients had been treated with tamoxifen and only one prior endocrine treatment was allowed.

The Committee noted that the primary efficacy measure of time to progression did not differ significantly between the treatment arms, being 5.5 months for fulvestrant. Other efficacy measures such as time to treatment failure, objective response rate and duration of clinical benefit also did not demonstrate any significant difference to anastrazole in the patient group. The Committee noted that by analysing the results with the duration of response set to zero for

non-responders the investigators were able to demonstrate a statistically significant advantage for fulvestrant.

The Committee noted that both treatments were relatively well tolerated with withdrawals from the study due to adverse events being 3.2% for fulvestrant and 1.3% for anastrazole. The incidence of thromboembolic events in patients treated with fulvestrant was 3.7%, which was higher than for patients treated with anastrazole. Quality of life measurement was maintained during the course of the study and did not differ between treatments.

In the second study, by Osbourne et al (Trial 0021), 400 patients were randomised to fulvestrant 250mg monthly (given in two aliquots) or anastrazole 1mg daily. A double-dummy approach was used to blind treatment received.

The study population was very similar to the population in the 0020 trial, with 95% of patients having received prior tamoxifen therapy.

The primary endpoint of time to progression was not different between treatment groups and most secondary measures also did not demonstrate any significant difference. The median duration of response could be shown to have a statistically significant benefit for fulvestrant, if the non-responders were assumed to have a duration of response of zero.

Both treatments were well tolerated. Injection site reactions were reported in 25% of patients and were not different between treatment arms (patients in the anastrazole arm received the injection vehicle).

A combined analysis of both studies demonstrated similar outcomes for both treatments, including median time to death in the extended 27-month follow-up.

The Committee considered that the available clinical data demonstrates that fulvestrant has a similar therapeutic benefit to anastrazole when administered to patients who have had prior tamoxifen therapy.

The Committee did not consider that the evidence demonstrated the efficacy of fulvestrant after failure of both tamoxifen and aromatase inhibitors, which was the indication proposed by the supplier.

The Committee noted the report of a compassionate use programme in Europe in which 339 patients were treated, with overall clinical benefit identified in 39%. The benefit diminished the further down the treatment sequence that fulvestrant was used.

The Committee considered that the sequencing of endocrine therapies is a critical issue in the management of advanced breast cancer. Fulvestrant is another option that could be used in the sequence, but it is not clear what the best place in therapy, or duration of therapy, would be. The Committee considered that if used as a last-line treatment the duration of therapy might be longer than the median of 5.5 months demonstrated in the studies, since treatment might continue after disease progression. The Committee also considered that it was not clear how this treatment would impact on the use of chemotherapy and was unsure if it would delay chemotherapy, in particular. All of these factors would be important in determining an estimate of cost-utility.

The Committee considered that despite the lack of evidence of efficacy following failure of two endocrine treatments, a third-line position for funding would be reasonable given the prognosis of the patient population [ ] The Committee also discussed the advantages and disadvantages of a monthly injection, rather than daily tablets. Overall the Committee considered that this delivery route would create some issues particularly given that it is a 5ml injection, which would be a large volume for intramuscular use (and in practice would probably need to be divided) and that such large intramuscular injections may adversely affect quality of life in what for many patients may be the terminal phase of their lives. It also noted that the intramuscular route for injection would need some training of community nurses to ensure that accidental subcutaneous injection is avoided. The Committee further considered that for Maori women in particular there may be some social issues around the treatment.

The Committee considered that advice should be sought from its Cancer Treatments Subcommittee on the place in treatment of fulvestrant. In the meantime the Committee **recommended** that the product should be listed as a third-line treatment for locally advanced or metastatic breast cancer and gave this recommendation 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, (vi) the budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Tiotropium bromide (Spiriva)

The Committee considered a further application from Boehringer Ingelheim relating to widening access to tiotropium for chronic obstructive pulmonary disease (COPD). Members noted that the Committee had considered applications relating to this several times previously and that the Committee had recommended widening access only if doing so would be cost-neutral.

Members noted the results of a post-hoc sub-analysis of the Vinken study and considered that this was relatively weak evidence in support of access widening, with both arms failing to reach statistical significance.

The Committee considered that the available evidence for tiotropium was across broad ranges of COPD, with a reduction in hospitalisations versus ipratropium. The Committee noted that the sub-analysis shows a general improvement in forced expiratory volume in one second (FEV_1), but not in other important outcomes, such as hospitalisations and clinical exacerbations.

The Committee noted that there is a lack of good evidence for tiotropium against appropriate comparators, such as inhaled long-acting beta-adrenoceptor agonists.

Members noted that the uptake of tiotropium in New Zealand since listing had been less than expected and that aggregated individual dispensing data indicated that there was a relatively high rate of drop-outs. Members noted that the availability of spirometers in general practices was unknown, but that it has been reported to be relatively low in certain areas.

The Committee **recommended** widening access to tiotropium by amending the FEV_1 limit in the Special Authority restriction from <40% of predicted to <60% as proposed.

The Decision Criteria relevant to this recommendation are *(i) the health needs of all eligible people within New Zealand, (ii) the particular health needs of Maori and Pacific peoples, (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 services.*

Movicol (Macrogol)

The Committee considered an application from Norgine Limited for the listing of Movicol (Macrogol 3350 with Sodium Chloride, Sodium Bicarbonate and Potassium Chloride) on the Pharmaceutical Schedule for the prevention or treatment of opioid-induced constipation for patients in a palliative care setting and for patients with malignant neoplasia.

The Committee considered that the application was of average strength and quality.

The Committee noted that the evidence provided did not specifically investigate patients with opioid-induced constipation in palliative care or patients with malignant neoplasia. The Committee noted that there was no evidence to compare Movicol to lactulose, which would be the principal comparator in New Zealand.

Members noted that Danthron with Polyaxomer had recently been discontinued from the New Zealand market and that some patients may benefit from an alternative treatment. The Committee noted that lactulose was currently the most widely used osmotic laxative. The Committee noted that many patients find lactulose unpalatable and it is associated with unwanted side effects, which leads to poor patient tolerability.

The Committee noted that there is currently a range of laxatives available fully funded in New Zealand, but noted that the burden of disease of constipation was relatively high.

The Committee considered that although the application was limited to opioid-induced constipation in palliative care and malignant neoplasia, Movicol may have benefit in other patient populations with constipation, especially the elderly and those with faecal impaction. Members noted that Movicol would also be beneficial in the treatment of paediatric patients.

The Committee considered that the cost offsets associated with the use of Movicol were likely to be substantially less than those estimated by the supplier.

The Committee also considered that although Movicol was substantially more expensive than lactulose, the budgetary impact of listing was likely to be manageable.

The Committee **recommended** that the application under the proposed access criteria be declined.

The Committee **recommended** that Movicol be listed on the Pharmaceutical Schedule, under Special Authority criteria reflecting a constipation treatment cascade to be developed by PHARMAC staff in consultation with relevant bodies, with a medium 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.*

Pegylated liposomal doxorubicin hydrochloride (Caelyx)

The Committee reviewed an application from Schering-Plough for the listing of pegylated liposomal doxorubicin hydrochloride (Caelyx, PLDH) on the Pharmaceutical Schedule for the treatment of advanced epithelial ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen.

The Committee noted that ovarian cancer is the fifth highest cancer type for incidence and the fourth highest for mortality amongst all cancers in New Zealand women, with increased incidence and mortality in Maori compared with non-Maori. The Committee noted that the prognosis for ovarian cancer was poor, as early-stage ovarian cancer is generally asymptomatic; therefore, most women present late with advanced stage disease when metastases may already be present.

The Committee noted that currently first-line treatment for ovarian cancer is usually surgery (with or without radiotherapy) followed by chemotherapy with a platinum agent (carboplatin or cisplatin), either alone or in combination with paclitaxel. However, the Committee noted that almost all patients relapse (70% after 2 years); therefore, second-line treatment is usually required, the goal of which is essentially palliative. Members noted that response to second-line treatment was dependent on platinum sensitivity. In some cases patients may respond to rechallenge with platinum agents, especially if they are platinum sensitive (relapse more than six months post first-line treatment) but alternative treatments may also be used alone, or in combination with platinum, including paclitaxel, docetaxel, gemcitabine and topotecan in platinum-resistant patients (relapse less than 6 months post first-line treatment). However, members noted that topotecan (Hycamtin, GSK) although registered in New Zealand, is not currently available

Members noted that PLDH is a pegylated liposomal formulation of doxorubicin hydrochloride, a cytotoxic anthracycline, that is thought to act by inhibiting DNA, RNA and protein synthesis.

The Committee considered data from two open-label, randomised active-comparator controlled trials (30-49 and 30-57). Trial 30-49 was a Phase III open-label RCT that enrolled 474 patients, most (73%) of whom had been treated with platinum and taxanes. Patients were randomised to receive PLDH 50 mg/m2 every 28 days (n=239) or topotecan 1.5 mg/m2 per day for five days every 21 days (n=235) (Gordon et al Gynaecologic Oncology 2004). At long-term follow-up (4-6 years) 87% of patients had died. Members noted that median overall survival in patients treated with PLDH was prolonged with a median survival of 62.7 weeks compared with 59.7 weeks in topotecan-treated patients (p=0.050, HR 1.216, 95% CI 1.0-1.478). However, there were no

statistically significant differences in median progression-free survival (16 weeks PLDH vs. 17 weeks topotecan) or response rates (19.7% PLDH vs. 17% topotecan).

The Committee noted that survival benefit for PLDH was much better in the platinum-sensitive patients (46% of the trial population): 108 weeks for PLDH vs. 70 weeks for topotecan (p=0.017, HR 1.432, 95% CI 1.066-1.923), but that there was no such survival difference in platinum-resistant patients.

Trial 30-57 was a Phase III open-label RCT comparing PLDH with paclitaxel that planned to enrol 438 taxane-naive patients; however, members noted that enrolment was terminated after only 216 patients were enrolled. Data were reported for adverse events and survival only. No statistically significant difference in median survival between the two treatment groups was reported (47 weeks in the PLDH group vs. 56 weeks in the paclitaxel group, HR = 0.931, 95% CI 0.70 – 1.23).

The Committee considered that the main treatment-related adverse effects of PLDH were severe skin reactions and stomatitis. The Committee considered quality of life data from study 30-49 demonstrated more pain in the PLDH treated patients compared with topotecan.

The Committee considered that PLDH may have a place in therapy for platinum-sensitive patients; however, given its high cost and unfavourable toxicity profile in what is essentially a palliative setting the Committee **recommended** that the application be declined.

The Committee **recommended** that this minute be presented to the Cancer Treatments Subcommittee for comment.

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.*

Bosentan (Tracleer)

The Committee reviewed a further application from Actelion in relation to bosentan for the treatment of pulmonary arterial hypertension (PAH). Members noted that there was little additional evidence provided in support of bosentan since the previous considerations by the Committee.

The Committee also noted a submission from the New Zealand Rheumatology Association. Members noted, however, that this submission was specific to bosentan, rather than PAH generally and that it contained no new information for the Committee's consideration.

Members noted that the Committee had viewed an application regarding bosentan in February 2005, whereupon a low priority recommendation was given.

The Committee noted that PHARMAC's review of high-cost treatments is currently underway and that decisions regarding bosentan may be affected by the outcomes of this review.

Members noted that the supplier's submission covered only idiopathic PAH and PAH secondary to scleroderma, the indications for which bosentan had been registered by Medsafe. The Committee noted that PHARMAC would realistically have to consider the management of all PAH patients, including PAH secondary to other connective tissue diseases and PAH secondary to congenital heart disease.

Members noted that the Committee had previously considered that the prevalence of PAH was 30-50 per million, which would result in perhaps 120-200 patients in New Zealand. Members noted that the supplier had estimated that there would be perhaps only 83 patients in New Zealand, although members noted that the supplier's estimates were based only on idiopathic PAH and PAH secondary to scleroderma.

The Committee noted that currently approximately 50 patients are funded through Exceptional Circumstances and that while some patients are on dual therapy, most are treated with sildenafil alone. Members noted that there appears to be approximately an even split between primary (idiopathic) and secondary PAH in Exceptional Circumstances patients.

The Committee noted the results of the study by Hoeper et al (Eur Respir J. 2005 Nov; 26(5): 858-63.), a three-year study involving 118 patients examining the benefits of a prescribed treatment algorithm for combination treatment. Members noted that by the end of follow-up, 43.2% of patients required dual or triple therapy.

The Committee noted that there were further data emerging on the benefits of combination treatments, mostly in New York Heart Association (NYHA) class III and IV patients.

The Committee considered the supplier's claims that bosentan is life-extending to be based on comparison of results from uncontrolled studies with historical control data, limiting their validity. However, better data for a serious and uncommon condition such as PAH may never become available.

Members noted that most available trials were not randomised and controlled and considered that there was a need for longer follow-up periods.

The Committee noted that the supplier had provided some comparative data between bosentan and sildenafil, which is not currently registered for PAH.

Members noted the results of the Seraph study (Am J Respir Crit Care Med. 2005 Jun 1; 171(11): 1292-7.), including 26 patients randomised to either bosentan or sildenafil. Members noted that the results of this small study indicated that sildenafil was significantly better than bosentan in improving six-minute walking distance.

Members noted that the supplier's estimated pricing of sildenafil was incorrect and grossly overestimated this cost.

The Committee noted that bosentan may have a teratogenic effect and that there are known issues with hepatotoxicity. Members noted that there were no data in the supplier's submission relating to decreased levels of haemoglobin.

The Committee noted the proposed management model produced by the supplier and considered that this had some merit. Members noted that a disease-state management panel

remains a possibility for pulmonary arterial hypertension, which could include one or more treatment options.

The Committee considered at this stage, however, that there was no reason to alter its previous **recommendation** of listing bosentan on the Pharmaceutical Schedule with a low priority. However, the Committee noted that PAH is a serious condition requiring planned treatment. The Committee **recommended** establishing a PAH panel in a timely manner to oversee the pharmaceutical management of patients with PAH.

Adalimumab (Humira) for psoriatic arthritis

The Committee considered an application from Abbott Laboratories to widen access to adalimumab on the Pharmaceutical Schedule for the indication of psoriatic arthritis.

The Committee noted the submission from the New Zealand Rheumatology Association entitled "New Treatments for Psoriatic Arthritis" that was reviewed by PTAC in August 2006.

The Committee considered that the placebo controlled trials provided were of good quality and moderate strength. The Committee noted that primary outcomes of ACR20 (American College of Rheumatology 20% Response Criteria) and PsARC (Psoriatic Arthritis Response Criteria) were achieved and were statistically significant in the key trials provided.

The Committee noted that the evidence showed a significant improvement in Quality of Life as measured by HAQ (Disability Index of the Health Assessment Questionnaire).

The Committee noted that there were no head-to-head trials for this indication comparing adalimumab with standard disease-modifying anti-rheumatic drugs (DMARDs), but considered that methotrexate and sulphasalazine showed limited efficacy in the treatment of psoriatic arthritis.

The Committee considered that there are no additional safety concerns associated with the use of adalimumab in psoriatic arthritis beyond those applying to all Tumour Necrosis Factor (TNF) alpha drugs across all indications.

The Committee noted its minute from August 2006 regarding the use of etanercept in psoriatic arthritis. The Committee reiterated that there was an unmet need for treatments for severe psoriatic arthritis unresponsive to DMARDs.

The Committee noted that there were no substantial head to head trials of etanercept against adalimumab and considered that either agent would be an acceptable treatment in psoriatic arthritis.

Members noted that it would be desirable to have more than one TNF inhibitor listed on the Pharmaceutical Schedule for the treatment of psoriatic arthritis.

The Committee **recommended** that either etanercept or adalimumab be listed on the Pharmaceutical Schedule with a medium to high priority for severe psoriatic arthritis refractory to standard treatments. The Committee considered that the listing of one agent should not preclude the listing of a second-line agent.

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, (iv) the clinical benefits and risks of pharmaceuticals 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.*

Adalimumab (Humira) for ankylosing spondylitis

The Committee considered an application from Abbott Laboratories to widen access to adalimumab on the Pharmaceutical Schedule for the treatment of ankylosing spondylitis (AS).

The Committee noted that the product was not yet approved for this indication and therefore it would not be able to make a recommendation about listing on the Pharmaceutical Schedule until such approval was given. The Committee also noted that it had considered another TNF-inhibitor for this indication.

The Committee pointed to relevant publications that had been omitted by the supplier (e.g. the review by Kavanaugh et al and the publication of trial 607), that the Committee had to source for itself.

The Committee noted that AS is a chronic inflammatory disease resulting in progressive ossification of ligaments in the spine and that it is associated with significant disability and reduced quality of life. It also noted that AS can be associated with a peripheral inflammatory arthritis, and that this is usually treated with DMARDs such as methotrexate.

The Committee noted that the condition is often not diagnosed and that the burden of disease is difficult to identify, with the prevalence being perhaps as high as 0.5-1%. The Committee noted the submission by the NZ Rheumatology Association and considered that the estimate of about 60-80 patients in NZ who might receive TNF treatment for this indication was reasonable. Such numbers would be consistent with the experience in Australia. The Committee did not consider that the number of patients treated would increase appreciably over time, due to the high drop-out rate expected.

The Committee noted that there are no drugs currently available that have been shown to be disease modifying in AS. Patients are managed currently with non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy. Methotrexate is also sometimes used, although data supporting its effectiveness for axial disease is lacking. The Committee considered that there is a need for a disease-modifying treatment, particularly for managing "end of spectrum" patients who have a significant burden in terms of reduced quality of life, although it noted that AS does not appear to affect survival.

The Committee considered the clinical evidence as it applies to the use of adalimumab in AS. The Committee noted that the data have follow-up only to 24 weeks, which makes determination of whether TNF modulators are disease-modifying in AS difficult.

The Committee noted the open-label MRI study in 15 patients by Haibel et al and did not discuss it further.

The Committee considered the studies by van der Heijde et al (Trial 607) and an unpublished study (Trial 606) involving 315 and 82 patients, respectively.

The Committee noted that the studies demonstrated an increased number of people treated with adalimumab compared with placebo reported a 20 or 50% improvement on the relevant composite scales, being the ASAS20 and the BASDAI 50 respectively (and also on the ASAS50 and ASAS70 as secondary measures).

The Committee discussed the clinical relevance and the subjectivity of these scales and considered that, while they showed efficacy in a clinical trial context, they would be of limited value as targeting criteria. The Committee considered that the ASAS5+6 scale may be a better measure since it contains objective components to the measurements (such as measurements of spinal mobility and inflammation).

In the report by van der Heijde et al, patients received 40 mg of adalimumab on alternate weeks as monotherapy (on the basis that methotrexate is not effective for spinal disease in AS). About 90% of patients enrolled did not have peripheral arthritis. The study reported an analysis at 12 weeks with extension for 24-week analysis. The Committee noted that 40% of patients in the adalimumab arm didn't get a response at 12 weeks and dropped out of the study.

The Committee noted that there was an absolute 36% benefit in patients meeting the ASAS20 threshold. There was a 29% absolute increase in the number of patients meeting the BASDAI50 outcome and 32.5% on the ASAS5+6 scale.

The supporting 606 study demonstrated a much higher non-response rate of around 60% at 12 weeks. There was a lower absolute treatment effect of about 23% on the BASDAI50 and a non-significant 20% on the ASAS20. The Committee noted that this was a small unpublished study and considered it supportive evidence. It did not consider that the pooled analysis provided by the supplier made any difference to the strength of the evidence as the Van der Heijde study was sufficiently powered and achieved its endpoints. Overall the Committee considered that the strength of the evidence for the therapeutic claims was moderate and the quality was good.

The Committee did not identify any unexpected safety issues although, as in other indications there would be concerns over activating latent TB and future risk of malignancies.

The Committee did not make a recommendation for listing adalimumab, pending the result of the regulatory submission (at which time it would review its recommendation). It did, however, consider that there was growing evidence of a clinically significant treatment effect from the use of TNF inhibitors in severe AS and **recommended** that PHARMAC fund such a treatment and gave its recommendation a medium priority, although the cost-utility was likely to be high in comparison with other potential investments.

The Committee also considered that advice on appropriate targeting criteria would be needed and recommended that PHARMAC staff seek advice from the NZ Rheumatology Association in this regard and bring the advice back to the Committee for a recommendation. The Committee considered that the criteria should target those patients that are most severely affected and not able to be managed with NSAIDS and physiotherapy.

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

Clopidogrel

The Committee considered a submission from PHARMAC staff regarding the addition of aspirin-naïve patients to the clopidogrel Special Authority criteria.

The Committee noted that clopdiogrel had been listed on the Pharmaceutical Schedule under Special Authority criteria and that PHARMAC staff had received a number of consultation responses requesting that aspirin-naïve patients be eligible for three months of clopidogrel if they have experienced:

1. an acute myocardial infarction, or

2. had an episode of pain at rest of greater than 20 minutes duration due to coronary disease that required admission to hospital for at least 24 hours, or

3. had a troponin T or troponin I test result greater than the upper limit of the reference range, or

4. had a revascularisation procedure.

The Committee noted that the indication for aspirin-naïve patients had previously been considered by PTAC but had not recommended for funding due to the potentially large number of patients and, therefore, potentially significant fiscal risk.

The Committee noted PHARMAC staff estimates of the number of patients and the resulting fiscal implications. The Committee also noted that at the current price of clopidogrel, it was cost-effective for aspirin-naïve patients to be eligible for clopidogrel under the proposed criteria.

The Committee considered that patients who would be eligible for clopidogrel according to the troponin T of troponin I criterion would be eligible according to the acute myocardial infarction criterion and therefore the former is redundant and should be removed from the Special Authority criteria.

The Committee **recommended** with a high priority that aspirin-naïve patients be eligible for three months of clopidogrel if they have experienced:

1. an acute myocardial infarction,

2. or had an episode of pain at rest of greater than 20 minutes duration due to coronary disease that required admission to hospital for at least 24 hours, or

3. had a revascularisation procedure.

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

Subcommittee Records

Cancer Treatments Subcommittee (CaTSoP) – 26 / 27 October 2006

PTAC noted and accepted the minutes of the Cancer Treatments Sub-Committee of PTAC (CaTSoP) meeting held on 26 / 27 October 2006, with the following comments:

PTAC was cognisant of the promising preliminary data for trastuzumab and the need for more effective treatment options in this patient population.

However, PTAC reiterated that there was still uncertainty about the best way of administering trastuzumab in terms of optimal treatment duration, dose and schedule (sequential to, or concurrent with, chemotherapy), minimising cardiovascular toxicity and long-term clinical outcomes.

PTAC noted CaTSoP's discussion and recommendations regarding trastuzumab. The Committee noted that PHARMAC's amended base-case cost-utility analysis resulted in an indicative cost/QALY of $12,300-$29,200 for 9 weeks trastuzumab treatment as equivalent to the FinHer trial regimen; however, the Committee noted that this did not include the additional cost of docetaxel that was used in FinHer. PTAC noted that the absolute disease-free survival for trastuzumab-treated patients in the FinHer trial was 89% at three years, whereas the published absolute disease free survival in the HERA trial was 86% (95% confidence interval 83%-89%) at a median duration of one year.

The Committee considered that more clinical research was needed and that a study comparing 12 months trastuzumab with 9 weeks trastuzumab should be performed.

The Committee noted CaTSoP's view that, in the absence of availability of funding for 12 months trastuzumab treatment, 9 weeks treatment would be reasonable. PTAC **recommended** that, subject to an acceptable cost/QALY, including the cost of docetaxel, 9 weeks treatment with trastuzumab should be funded and gave this recommendation a high priority.

The Committee considered that the relevant decision criteria in favour of this recommendation were *(i) the health needs of all eligible people within New Zealand, (ii) The particular health needs of Maori and Pacific peoples (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 and (viii) the Government's priorities for health funding.*