

August 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.

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Record of PTAC meeting held 24 & 25 May 2006

PTAC reviewed the record of the PTAC meeting held on 24 & 25 May 2006 and made the following minor amendment:

Etanercept & infliximab for second-line tumour necrosis factor alpha inhibitor treatment of Rheumatoid Arthritis – paragraph 15.12: insert “*The Decision Criteria relevant to this recommendation are: (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things, and (iv) The clinical benefits and risks of pharmaceuticals.*”

Matters Arising

Clopidogrel Special Authority criteria

PTAC was consulted on some aspects of the proposed clopidogrel Special Authority criteria after the consultation letter to list Plavix was sent out.

PTAC members noted a consultation letter that stated that patients who had not completed six months clopidogrel treatment under the post-stenting criteria, and were therefore on clopidogrel and aspirin, who experienced a documented stent thrombosis were not eligible for lifetime clopidogrel. However, patients who had completed six months clopidogrel treatment under the post stenting criteria and who while on treatment with aspirin experienced a documented stent thrombosis were eligible for lifetime clopidogrel. PTAC members considered that patients who experienced documented stent thrombosis while on treatment with clopidogrel and aspirin should also be eligible for lifetime clopidogrel and **recommended** that the initial application criteria for documented stent thrombosis should be altered as follows (change in strikethrough).

The patient has, while on treatment with aspirin, experienced documented stent thrombosis ~~after stopping clopidogrel.~~

PTAC members also considered a consultation response asking that clopidogrel be available for three months, for patients who have a positive cardiac marker (troponin positive) even if they were not on aspirin. PTAC members considered that patients who experience a cardiac event should receive aspirin initially, and if they had a further event whilst on aspirin then they should be eligible for clopidogrel. PTAC **recommended** that the proposed alteration to the Special Authority not be included.

PTAC members noted that PHARMAC staff had widened the access criteria to include application by general practitioners as well as specialists and considered that this was appropriate.

PTAC members noted that PHARMAC staff had altered the renewal criteria for aspirin tolerant patients from "the patient has experienced an additional vascular event within 2 weeks of stopping clopidogrel" to "the patient has experienced an additional vascular event following the recent cessation of clopidogrel". The PTAC members considered that this was appropriate.

PTAC members discussed whether peripheral vascular disease should be included in the clopidogrel criteria. They noted that peripheral vascular disease was associated with an increased risk of cardiovascular and cerebrovascular events and that the CAPRIE study showed

that clopidogrel reduced further cardiac events in patients with peripheral vascular disease. PTAC therefore **recommended** that symptomatic peripheral vascular disease be added to the aspirin allergic criteria.

PTAC members also recommended that a revascularisation procedure be added to the criteria for aspirin allergic patients.

Levonorgestrel implants (Jadelle) for contraception

The Committee considered a submission from Schering for the listing of levonorgestrel implants (Jadelle) on the Pharmaceutical Schedule. The Committee noted that the application was of poor quality. Members noted that most of the papers contained within the submission were not relevant to contraceptive implants, and of those that were, only one paper related directly to Jadelle. Members were, however, aware of other data available on the Population Council website. The Committee noted that the application from Schering appeared to focus strongly on the applicability of the product to teenage women.

The Committee considered that levonorgestrel implants appeared to be a useful additional contraceptive, but noted that, unlike other contraceptive options, levonorgestrel implants can only be used for contraceptive purposes. Population Council trials suggest that Jadelle is one of the most effective reversible contraceptives available with a cumulative pregnancy rate of 1.1% after five years (although the rate is higher in women greater than 60 kg). Members noted that levonorgestrel implants appear to have a lower failure rate than oral contraceptives, and similar to sterilisation. Members noted the studies by Sivin et al (Contraception. 1997 Feb; 55(2): 73-80.) and Wang et al (Adv Contracept. 1992 Jun; 8(2): 105-14.), which indicated that levonorgestrel implants appeared to have similar efficacy to each other, and to levonorgestrel-releasing intra-uterine devices.

Members noted that levonorgestrel implants had a modest 41.5% 5-year continuation rate, with a high rate of discontinuation due to adverse events – 14.1% for menstrual irregularities and 14.7% for other medical reasons (headaches, depression, weight gain or hair loss). Overall, 65% of patients reported menstrual irregularities.

The Committee noted that levonorgestrel implants appeared to be associated with a moderate rate of local reactions, with one study indicating that 15.6% of patients experienced an application site reaction, such as discoloration, pain or itching. There have also been associated problems with removal of the rods (1.5%) which may be higher when attempted by a non-expert group of practitioners. Members also noted that levonorgestrel implants are associated with higher rates of gall bladder disease and hypertension compared with non-hormonal contraceptives, but that there were lower rates of ectopic pregnancy and pelvic inflammatory disease when compared to intra-uterine devices.

Members considered that the effect of levonorgestrel implants on bone mineral density was unclear. Members noted that although the supplier had indicated that there is no effect, which is supported by a recent WHO statement on progestogens, one recent study indicated that there is a reduction in BMD in the ulna shaft after 18-36 months.

The Committee noted that the insertion and removal of levonorgestrel implants are both minor surgical procedures that would be associated with significant costs to patients. Members disagreed with the supplier's assessment that there are significant ongoing costs to patients associated with intra-uterine devices. The Committee considered that the costs associated with

the insertion and removal of levonorgestrel implants may deter those patients who could benefit most.

Members noted that the proposed pricing of Jadelle is significantly higher than the cost of five years of oral contraception.

The Committee noted that although Schering had posited that there could be downstream savings to District Health Boards from levonorgestrel implants, there was no evidence provided in support of such claims. Members also noted that Schering had not accounted for the costs associated with the treatment of implant-associated menorrhagia.

The Committee noted that New Zealand has high teenage pregnancy and abortion rates. However members further noted that a New Zealand survey (N Z Med J. 1994 May 25; 107(978): 189-92.) indicated that a large proportion (39%) of unwanted pregnancies were due to an absence of contraception, rather than a failure of contraceptive methods.

Members noted that there is a high uptake of medroxyprogesterone acetate depot in Maori and Pacific Island populations, and that there are often problems with follow-up administrations. Members considered that the acceptability of levonorgestrel implants in these communities could be explored further. The Committee noted that there was little data to indicate whether the efficacy of levonorgestrel implants is affected in patients with a larger body mass, or with larger amounts of subcutaneous arm fat.

Members noted that not all clinicians would be able to provide an insertion and removal service for levonorgestrel implants.

The Committee **recommended** that levonorgestrel implants be listed on the Pharmaceutical Schedule with a medium priority.

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, (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services, (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 (vii) the direct costs to health service users.*

Tenofovir disoproxil fumarate (Viread) – supplementary information

The Committee reviewed a supplementary submission from Gilead Sciences for the listing of tenofovir disoproxil fumarate (Viread) with or without emtricitabine (Emtriva) on the Pharmaceutical Schedule for use in treatment-naïve and -experienced patients with HIV.

The Committee noted that tenofovir is a nucleotide reverse transcriptase inhibitor (RTI), considered by the Committee to have similar therapeutic effects to nucleoside RTIs. The committee noted that previously it recommended that tenofovir be listed for use in treatment-experienced patients with HIV with a moderate priority.

The Committee noted that emtricitabine is a derivative of lamivudine. The Committee noted that previously it recommended that emtricitabine be declined primarily due to lack of additional efficacy benefit over lamivudine and the possibility of additional side effects.

The Committee considered that this submission provided new clinical evidence on the use of both tenofovir and emtricitabine in treatment-naïve HIV patients.

The Committee reviewed data from one new open label non-inferiority study, Study 943. The Committee considered that this study, which enrolled 517 treatment-naïve HIV infected patients, was of high quality and of moderate strength. The Committee noted that in this study patients were randomised to receive either tenofovir and emtricitabine (n=255) or fixed dose Combivir (zidovudine plus lamivudine) (n=254), both in combination with efavirenz.

The Committee noted that at 48 weeks significantly more patients on tenofovir and emtricitabine reached the primary endpoint of HIV RNA <400 copies per mL compared with patients on Combivir (84% vs 73%). The Committee considered that differences in favour of the tenofovir and emtricitabine treatment group were evident across all the efficacy endpoints presented.

The Committee noted that withdrawal due to adverse events was higher and adherence was lower in the Combivir treatment group. The Committee also noted that in a subgroup of patients DEXA scanning indicated that total limb fat was lower and that lipid levels were marginally higher in patients treated with Combivir.

The Committee noted that tenofovir is currently in development for the treatment of chronic Hepatitis B and may prove to be of particular use in HIV/Hepatitis B co-infected patients.

The Committee also noted that tenofovir may be of particular use in treatment-experienced patients taking the fusion inhibitor enfuvirtide (Fuzeon), to be listed on the Pharmaceutical Schedule from 1 September 2006, which must be administered with optimised background therapy (OBT) including at least one new antiretroviral drug to which the patient has never previously been exposed.

The Committee considered that in light of the new evidence provided its previous recommendations for both tenofovir and emtricitabine should be reconsidered.

The Committee **recommended** that tenofovir be listed on the Pharmaceutical Schedule with a moderate priority for use in treatment-experienced and treatment-naïve HIV-infected patients and with a high priority for treatment of patients with HIV/Hepatitis B co-infection.

The Committee further **recommended** that emtricitabine be listed on the Pharmaceutical Schedule with a moderate priority.

The Decision Criteria relevant to these recommendations 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.*

Pemetrexed disodium (Alimta)

The Committee reviewed a submission from Eli Lilly for the listing of pemetrexed disodium (Alimta) on the Pharmaceutical Schedule for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior platinum-based chemotherapy (second line).

The Committee noted that the Cancer Treatments Subcommittee of PTAC (CaTSOP) had previously reviewed an application for pemetrexed for the treatment of patients with malignant pleural mesothelioma in combination with cisplatin. The Committee noted that CaTSOP recommended pemetrexed be listed on the Pharmaceutical Schedule for malignant pleural mesothelioma with a low priority and PTAC had endorsed this recommendation.

The Committee noted that this submission was based on one open label phase 3 trial (JME1, J Clin Oncol. 2004 May 1;22(9):1589-97) comparing docetaxel with pemetrexed in patients with stage IIIb or IV NSCLC. All patients had received prior chemotherapy; approximately 90% received prior platinum-based chemotherapy.

The Committee considered that there was no difference between pemetrexed and docetaxel in any of the efficacy endpoints presented. Median survival time was 8.3 months for docetaxel compared with 7.9 months for pemetrexed. The one-year survival rate was 29.7% for both treatment groups. The Committee also noted that quality of life analysis was similar between the two treatment arms.

The Committee considered that the major difference between pemetrexed and docetaxel was a different side effect profile. The Committee noted that in this study there was increased haematological toxicity and hospitalisation due to neutropenic sepsis in the docetaxel-treated patients compared with pemetrexed.

The Committee noted that the supplier claimed that the increased cost of pemetrexed, compared with docetaxel, would be offset by the costs associated with hospitalisation and administration of granulocyte colony-stimulating factors (G-CSF) and antibiotics associated with the increased incidence of neutropenic sepsis in docetaxel treated patients. However, the Committee commented that the incidence of neutropenic sepsis reported in this trial for pemetrexed treated patients was significantly lower than has been reported in other trials. The Committee also noted that there was significant cross over between the two treatment groups during the study, and that overall there were more hospital stays in the pemetrexed treated patients compared with docetaxel (1772 vs. 1410 bed days)

The Committee did not consider that the difference in the adverse effect profile justified the additional expenditure for pemetrexed compared with docetaxel. The Committee **recommended** that the application be declined on the basis that the evidence showed no additional efficacy benefit of pemetrexed compared with docetaxel which is currently funded for second-line treatment of NSCLC.

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.*

Deferasirox (Exjade)

The Committee considered an application from Novartis for the listing of deferasirox (Exjade) on the Pharmaceutical Schedule for the treatment of patients with chronic iron overload.

The Committee considered that the application was of good quality, but that the evidence provided was limited.

The Committee noted that the evidence was based largely on study 107, a 12 month randomised controlled trial comparing desferrioxamine against deferasirox. The Committee considered that the primary end point used to indicate non-inferiority, Liver Iron Count (LIC), had not been met satisfactorily.

The Committee considered that outside of a clinical trial setting, deferasirox would not provide an equivalent therapeutic benefit compared to desferrioxamine

However, the Committee considered that deferasirox provided a major compliance and patient tolerability benefit over desferrioxamine infusion as it is an oral presentation and, therefore, not associated with infusion-related side effects or the logistic barriers to infusion treatment.

The Committee noted that use of deferasirox would result in a reduction in the infusion services required and may represent a saving to DHB service budgets.

The Committee considered that the cost of deferasirox represented a substantial financial risk to the Pharmaceutical Budget as there was major potential for use in inappropriate therapeutic settings such as myelofibrosis and haemochromatosis.

The Committee considered that it was imperative that deferasirox be targeted to the most appropriate patient group under Special Authority Criteria.

The Committee considered that children and thalassaemic patients suffering from chronic iron overload would have the most potential to gain benefit from this treatment.

The Committee considered that restricting use to *transfusional* iron overload would adequately target treatment.

The Committee **recommended** that deferasirox be listed on the Pharmaceutical Schedule with a high priority for the following patient groups:

- Adults with transfusional chronic iron overload where desferrioxamine is either not tolerated or contraindicated; or
- Children with chronic iron overload.

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.*

Etanercept (Enbrel) in Psoriatic Arthritis

The Committee considered an application from Wyeth Pharmaceuticals to widen the access criteria of etanercept (Enbrel) to include the indication of psoriatic arthritis. The Committee considered that the application was of good strength and quality.

The Committee noted study 16.0030, a phase III double blind, randomised control trial; and 16.0612, a phase II double blind, randomised control trial, were the pivotal studies in the application.

The Committee noted that the studies showed significant reductions in all levels of ACR (American College Rheumatology) measure of disease, and significantly higher PsARC (Psoriatic Arthritis Response Criteria) in patients with etanercept compared with placebo.

The Committee also noted that the studies indicated that treatment of Psoriatic Arthritis with etanercept was associated with significant improvement in Quality of Life as measured by the HAQ instrument against placebo.

In addition to the application the Committee considered a submission from the New Zealand Rheumatology Association (NZRA) regarding treatments for psoriatic arthritis available in New Zealand. The Committee noted that the submission provided a useful and objective overview of current and proposed treatments for psoriatic arthritis in New Zealand.

The Committee accepted the estimates provided that there are approximately 150 to 230 patients in New Zealand with severe psoriatic arthritis and who might benefit from treatment with a TNF-alpha inhibitor.

The Committee considered that there was an unmet need for treatments for severe psoriatic arthritis unresponsive to disease-modifying anti-rheumatic drugs (DMARDs). The Committee noted that it is standard rheumatology practice to use DMARDs, mostly sulphasalazine and methotrexate, in a similar way to their use in rheumatoid arthritis, even though none is listed for this indication.

The Committee considered that some patients may be gaining funded access to leflunomide treatment for psoriatic arthritis under the current Special Authority Criteria, but noted that the criteria did not specifically indicate psoriatic arthritis as an entry criterion. It considered that leflunomide should be used before a TNF-alpha inhibitor, but that there was a potential problem with the Special Authority criteria because leflunomide is not indicated for psoriatic arthritis in New Zealand. The Committee considered this difficulty could be addressed by changing the wording of the Special Authority criteria for leflunomide from "Rheumatoid Arthritis" to include "Inflammatory Arthritis". It noted that this widening of access was requested in the NZRA submission.

The Committee noted that in the treatment of rheumatoid arthritis, etanercept had a similar therapeutic effect to other TNF inhibitors. The Committee noted that it had not reviewed any applications for other TNF inhibitors in psoriatic arthritis, and that it would welcome such applications.

The Committee considered that PHARMAC staff should continue to seek advice from the NZRA to develop targeted Special Authority Criteria for a TNF Inhibitor for the indication of Psoriatic Arthritis.

The Committee **recommended** that etanercept be listed on the Pharmaceutical Schedule with a medium priority for the treatment of psoriatic arthritis.

The Decision Criteria relevant to these recommendations 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.*

Everolimus (Certican)

The Committee reviewed a submission from Novartis for the listing of everolimus (Certican) on the Pharmaceutical Schedule for the prophylaxis of organ rejection in patients following allogeneic renal or cardiac transplant.

The Committee noted that everolimus is a derivative of sirolimus but with a shorter half-life.

The Committee noted that the submission was based on several studies. Two double-blind studies compared everolimus with mycophenolate mofetil (MMF), used in combination with cyclosporine and steroids, in renal transplant patients (Am J Transplant. 2005 Oct; 5(10):2521-30, Transplantation. 2005 Jul 27;80(2):244-52). The Committee considered that the studies showed that everolimus was as effective as MMF in the prevention of organ rejection in both studies in terms of 3 year graft and patient survival.

One randomised, double-blind study compared everolimus with azathioprine, used in combination with cyclosporine and steroids, in cardiac transplant patients (N Engl J Med. 2003 Aug 28;349(9):847-58). The Committee considered that the data showed that everolimus was more effective than azathioprine in reducing the primary efficacy endpoint, a composite of graft loss, retransplantation or death at six months. However, patient survival at four years was similar and creatinine levels at six months were significantly higher in the everolimus treated patients. The Committee noted that everolimus reduced cardiac allograft vasculopathy; however the long term clinical benefit of this was unclear. The Committee noted that in this study no long-term graft survival data was available.

The Committee noted that the most important adverse effects associated with everolimus included hypertriglyceridaemia, hypercholesterolaemia, delayed wound healing, lymphocoeles, thrombocytopaenia, leucopaenia and haemolytic uraemic syndrome.

The Committee noted that no head to head studies comparing everolimus with sirolimus were presented. The Committee also noted that although studies of calcineurin inhibitor (CNI) dose reduction were presented, in contrast to sirolimus, no studies of CNI withdrawal had been presented.

The Committee considered that the place in therapy for everolimus was not clear. Members considered that most likely its place would be in CNI withdrawal regimens, or for renal rescue; however, this data was not available. The Committee also noted that the rates of organ transplantation are higher in Maori and Pacific Island people compared with Europeans; however, no data demonstrating treatment effect in Maori and Pacific Island people were presented.

Committee **recommended** that the application be declined because the place in therapy for everolimus was not clear at this time. The Committee **recommended** that its minute be presented to the Transplant and Immunosuppressant 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.*

Azithromycin for CF patients

The Committee reviewed a submission from clinicians for the widening of access to azithromycin for the treatment of patients with Cystic Fibrosis (CF) chronically infected with *Pseudomonas aeruginosa*.

The Committee noted that the Cystic Fibrosis Advisory Panel had reviewed the application from Professor Grimwood and related correspondence from the Cystic Fibrosis Association of New Zealand, at its meeting in April 2006. The Panel recommended that azithromycin be funded on the Pharmaceutical Schedule for patients with CF and chronic infection with *Pseudomonas aeruginosa*.

The Committee considered that studies have shown that azithromycin is effective in reducing decline in lung function, pulmonary exacerbations and antibiotic usage in patients with Cystic Fibrosis. The Committee noted that the optimum dose was unresolved but is likely to be around 500 mg daily in adults, although 3 times weekly dosing had been suggested by the Cystic Fibrosis Panel.

The Committee noted that the exact mechanism of action of azithromycin in this setting was unclear. The Committee considered that other macrolides may have a similar therapeutic benefit in Cystic Fibrosis patients; however, clinical evidence was based on studies with azithromycin.

The Committee considered that the Special Authority Criteria suggested by the Cystic Fibrosis Panel were reasonable; however, members considered that it should not exclude lung transplantation and that it was likely that there would be demand for treatment of bronchiectasis from causes other than Cystic Fibrosis.

The Committee noted that currently azithromycin is listed on the pharmaceutical schedule, with a restriction of two tablets, for patients with uncomplicated urethritis or cervicitis proven or presumed to be due to *Chlamydia trachomatis* and their sexual contacts. The Committee noted that it was not possible to have a specific Special Authority criterion or restriction for Cystic Fibrosis incorporated into the current restriction without either removing the current restriction on the number of tablets per prescription or removing the endorsement restriction. The Committee considered that it was important to maintain the 2 tablet restriction on azithromycin in the Pharmaceutical Schedule in order to limit its use outside of urethritis or cervicitis.

The Committee also noted that azithromycin is not indicated for the treatment of Cystic Fibrosis and a caution against use in Cystic Fibrosis patients is noted in the datasheet, although this caution related to use of azithromycin as an antibiotic.

Therefore, the Committee considered that it was not appropriate to alter the restrictions for azithromycin to permit treatment for Cystic Fibrosis through the Pharmaceutical Schedule. However, the Committee supported making funded access to azithromycin available to CF patients. The Committee considered it more appropriate that the Cystic Fibrosis Panel administer a funding mechanism for azithromycin for Cystic Fibrosis patients.

Nebulised Hypertonic Saline for Cystic Fibrosis

The Committee considered a proposal from the Cystic Fibrosis Advisory Panel for the listing of hypertonic saline on the Pharmaceutical Schedule for the treatment of cystic fibrosis.

The Committee noted the results of a study by Elkins et al (N Engl J Med. 2006 Jan 19; 354(3): 229-40.) examining nebulised 7% sodium chloride solution administered over a 48-week period in a sample of 164 patients with cystic fibrosis. Members noted that there was a small but statistically significant increase in FEV₁ of 68 mL, and a decrease in exacerbations of 1.42 per patient over the period.

Members noted that the available evidence for hypertonic saline indicated that there appears to be an early response to hypertonic saline and that the response is worse in patients with lower baseline lung function.

The Committee noted that the taste of hypertonic saline may cause compliance problems with children, and queried whether the taste could be masked as part of the compounding process.

Members noted that as most patients are likely to be in possession of a nebuliser already, additional costs associated with hypertonic saline are likely to be low. Members noted that hypertonic saline should be administered in combination with bronchodilator pre-treatment.

The Committee **recommended** making hypertonic saline available on the Pharmaceutical Schedule for the treatment of cystic fibrosis, with a medium-to-high priority.

Members also noted that, if listed in the Pharmaceutical Schedule, failure of prior treatment with hypertonic saline could be used as part of future criteria for access to dornase alfa.

Dornase Alfa for Cystic Fibrosis

The Committee considered a proposal from the Cystic Fibrosis Advisory Panel for widening the access criteria for dornase alfa to allow for treatment where forced expiratory volume in one second (FEV₁) is less than or equal to 75% of predicted.

Members noted that the current criteria allow for treatment in patients with an FEV₁ less than or equal to 65% of predicted.

Members noted that in 2003 the Committee had considered a proposal from the Panel in relation to dornase alfa, which was subsequently declined. The Committee noted that this proposal was an amendment to the previous proposal, based largely on the same information.

The Committee noted that there appeared to be some evidence of benefit from earlier treatment with dornase alfa, and that side effects were typically transient and mild. Members noted, that widening access to dornase alfa may result in it replacing hypertonic saline as early treatment for cystic fibrosis.

The Committee considered that there was insufficient evidence to change the access criteria for dornase alfa, and **recommended** that the proposal be declined.

Fentanyl patches for patients with severe pain of malignant origin

The Committee reviewed a submission from Janssen-Cilag to widen access to fentanyl transdermal patches (Durogesic) to include patients with severe pain of malignant origin, in addition to the current criteria (patient is terminally ill and is opioid-responsive and either is unable to take oral medication or is intolerant to morphine or morphine is contraindicated). The Committee noted that the supplier had also requested that approvals and renewals be valid for six months rather than three months.

The Committee noted that the supporting information from the supplier was limited, and consisted of a one-page letter expressing concerns from the oncology and palliative care communities. The Committee noted that fentanyl was an established agent and already subsidised.

The Committee noted that fentanyl was similar in action to morphine, oxycodone and methadone.

The Committee noted that methadone and oxycodone were options for patients who can swallow but who are intolerant to morphine or for whom morphine is contraindicated. The Committee noted that a subcutaneous morphine pump could be used in patients who cannot swallow but can tolerate morphine and for whom morphine is not contraindicated.

The Committee noted that the only alternative aside from fentanyl patches for patients who cannot swallow and are intolerant to morphine or for whom morphine is contraindicated is methadone infusion, but that opioid dose conversion and dose titration are difficult, and the long half-life can lead to drug accumulation.

The Committee noted that many terminally ill patients were elderly and could not tolerate high doses of fentanyl. The Committee considered that it would be useful to have a lower, 12.5 mcg per hour fentanyl patch available for starting dose and paediatric patients.

The Committee noted that there is currently no safe alternative opioid analgesic to fentanyl transdermal patches in patients with renal failure.

The Committee noted that fentanyl has fewer side effects than long-acting morphine, including less constipation and less sedation. The Committee also noted that the risk of overdose was higher with fentanyl because there is a smaller margin of error in dosing compared to morphine.

The Committee considered that access to fentanyl might be limited in patients in remote/rural areas without access to a "relevant specialist".

The Committee considered the current Special Authority criteria for access to fentanyl patches and felt that if a patient is intolerant to morphine or for whom morphine is contraindicated, the patient should not necessarily be required to be opioid responsive.

The Committee considered that the criteria should be altered to include intolerance to oxycodone and oxycodone contraindication in addition to intolerance to morphine and morphine contraindication.

Committee members considered that it might be appropriate to widen access to include patients with severe pain of malignant origin. Committee members noted that, if this were to happen, there appeared to be no compelling clinical reason why access should not also be widened to include patients with severe pain of non-malignant origin. The Committee considered that there might be other patient groups, such as those with severe pain and renal failure, who would benefit from fentanyl transdermal patches. The Committee noted the potential for abuse if access was widened too broadly.

The Committee considered that three months was an appropriate length of time for Special Authority applications and renewals to remain valid if access was restricted to terminally ill patients, but that six months might be more appropriate if access was widened to include non-terminal patient groups.

The Committee **recommended** that the application be referred to the Analgesic Subcommittee for further advice regarding the Special Authority criteria.

Herceptin new data

PTAC has twice considered trastuzumab for the treatment of early HER-2 positive breast cancer at its meetings of February and May 2006. These minutes should be read in conjunction with the February and May 2006 minutes found at <http://www.pharmac.govt.nz/pdf/ptacmins.pdf>

The Committee reviewed further information in support of a submission from Roche Pharmaceuticals for the listing of trastuzumab (Herceptin) on the Pharmaceutical Schedule for the treatment of early HER-2 positive breast cancer.

The Committee reviewed the following material:

Roche Pharmaceuticals' response to previous PTAC and CaTSOP minutes regarding trastuzumab;

A technology appraisal from the University of Sheffield School of Health and Related Research (SchHARR) commissioned by the National Institute of Clinical Excellence (NICE);

Two year median follow-up of the one year treatment arm of the HERA trial in the format of a PowerPoint slide presentation from the American Society of Clinical Oncology (ASCO) 2006 conference;

"Adjuvant Docetaxel or Vinorelbine with or without trastuzumab for Breast Cancer", *Heikki Joensuu et al.* (N Engl J Med 354;8, February 23 2006), the "FinHer study".

Correspondence from Roche Pharmaceuticals

The Committee noted Roche New Zealand's willingness to assist PHARMAC in the provision of evidence to support the use of trastuzumab.

The Committee expressed disappointment that additional trial data is unlikely to be available in a peer reviewed, published format in the near future.

SchARR report

The Committee noted that the SchARR report was very comprehensive and raised similar concerns regarding the costs and benefits of trastuzumab that had been highlighted in PHARMAC's own cost utility analysis and previous PTAC minutes.

Members noted that the final recommendation of the SchARR report did not appear to correlate to specific findings of the report.

ASCO 2006 slide presentation for the HERA study

The Committee noted the limitations of clinical data presented as a PowerPoint slide presentation, which have not been subjected to external peer review for a reputable scientific journal. The Committee reiterated its view that it does not consider slide presentations alone to be adequate for the purpose of making important clinical recommendations.

The Committee noted that after a median follow-up of one year, as presented in Piccart-Gebhart et al (N Engl J Med. 2005 Oct 20; 353(16): 1659-72.), there was a reported absolute increase in two-year disease-free survival of 8.4% in the trastuzumab arm compared with control. The Committee noted that the slides indicated that after a median follow-up of two years the absolute increase in disease-free survival at three years in the trastuzumab arm compared with control had been reduced to 6.3%.

The Committee noted that the slides indicated that after two years follow-up the absolute overall survival difference at three years from randomisation, as displayed, was 2.7% in the trastuzumab arm against control, and appeared to be statistically significant. Members noted that this translated into a number needed to treat (NNT) of 37 patients.

The Committee considered that in an adjuvant setting an ongoing treatment effect would be expected with efficacy differences becoming greater over time. The Committee considered, however, that the difference in the HERA treatment groups would have been anticipated to continue to diverge, rather than converge, which appears to be the case from the slide data presented. The Committee noted that 861 patients in the non-trastuzumab arm switched to trastuzumab after 12 months. Members noted that some of the convergence seen may have been due to the loss of patients from the observation arm, although there was insufficient data presented in the slides to clarify this.

Members noted that switching of patients from the observation arm to trastuzumab treatment meant that the validity of the long-term efficacy and safety profile of trastuzumab from the HERA trial may be significantly compromised. Members noted that although half of the patients in the observation arm who had not switched over by two years would be able to be measured in subsequent years, they would no longer necessarily be representative of all patients randomised to the observation arm. Members noted that this inconsistency would only be

rectified by maintaining intention-to-treat analysis of the efficacy of trastuzumab beyond the one year.

The Committee noted that in data presented as 'censored', (data that excluded patients who had switched from control to trastuzumab), the denominators were not small enough to account for removal of all switched patients. The Committee concluded that this apparent inconsistency would likely be addressed in a formal peer-reviewed publication of this data and highlighted the difficulties of evaluating clinical data from a slide presentation.

The FinHer study

The Committee considered that the FinHer study cast doubt over the optimal duration and timing of trastuzumab treatment. The Committee noted that the cost utility of trastuzumab use as per the FinHer protocol (9 weeks treatment) was likely to be appreciably better than 12 months treatment.

The Committee considered that the number of patients treated in the FinHer study (232) was substantial compared to many other cancer treatment trials.

The Committee noted that although HERA was a far larger trial, the number of patients treated in FinHer was not insignificant, and therefore the data from FinHer was valuable.

The Committee considered that the trastuzumab regimen used in the FinHer study resulted in comparable health gains to the regimen used in the HERA trial (11.7% absolute reduction in disease recurrence at three years against no trastuzumab), but produced less cardiotoxicity and other side effects, and was associated with a significantly reduced pharmaceutical and service cost.

The Committee considered that funding of trastuzumab as per the FinHer protocol (9 weeks treatment) could be considered.

Recommendations

The Committee recommended that the application for the funding of trastuzumab as per the HERA protocol (12 months treatment) be declined due to the uncertainty surrounding long term clinical benefits and risks; the uncertainty over optimal duration of treatment; and the high budgetary impact associated with treatment.

The decision criteria relevant to PTAC's recommendation were: (i) The clinical benefits and risks of pharmaceuticals; (v) the cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget).

The Committee **recommended** that the application be referred back to the Cancer Treatment Subcommittee of PTAC to consider the clinical appropriateness of any funding regimen consistent with the FinHer protocol (9 weeks treatment).

Growth hormone for adult patients

The Committee noted that the PHARMAC Board had directed PHARMAC Staff to find a way of funding individuals in whom Growth Hormone treatment was appropriate. This direction followed on from a Board decision not to fund growth hormone for an individual patient under the Exceptional Circumstances scheme. PHARMAC staff requested a view from PTAC on the appropriateness of introducing a programme involving “N of 1” trials, or some other way of identifying those individuals who would derive significant benefits from treatment.

PTAC reconfirmed its earlier statement that there is a group of growth hormone deficient adults in whom treatment with growth hormone would be beneficial.

The Committee reviewed a number of additional papers, which suggested increasingly important physiological benefits of replacement therapy in adults, in particular improvements in cardiac function, improved muscle tone and body composition as well as improvements in mood. However, the trials did not demonstrate a reduction in mortality rates and neither did they show consistent improvements in patients’ quality of life scores. The committee noted that the lack of significant benefits demonstrated in the trials may reflect the study design, patient selection or the robustness of the scales used to determine the impacts.

The Committee noted that the Exceptional Circumstances scheme had not worked as an appropriate mechanism for identifying those patients most likely to benefit. The Committee accepted that it was too difficult for the Exceptional Circumstances Panel to identify those patients who truly met the rarity criteria, such that they could be funded whilst other similar adults who were growth hormone deficient were denied funding.

The Committee noted that having a programme in place using “N of 1” trials would be interesting but may be practically difficult given the need for placebo controls. It noted the proposed criteria supplied by the NZ Society of Endocrinologists and noted that such criteria were potentially useful. The committee **recommended** that a subcommittee of PTAC be established to identify entry and exit criteria for access to growth hormone therapy for adults with severe sequelae from growth hormone deficiency.

The Decision Criterion relevant to this recommendation is: (i) *the health needs of all eligible people within New Zealand.*