

May 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 16 & 17 February 2006

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

Erythropoietin for oncology patients – paragraph 15.1: replace “improve patient’s response” with “improve a patient’s response”.

Erythropoietin for oncology patients – paragraph 15.2: replace “could compensate oxygen delivery” with “could compromise oxygen delivery”.

Prednisolone acetate – paragraph 16.5: replace “sub-grouped as recommended” with “sub-grouped according to potency as recommended”.

Goserelin – paragraph 19.10: insert “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*, (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*, (vii) *The direct cost to health service users*, and (viii) *The Government’s priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC’s Funding Agreement, or elsewhere*”.

Aromatase Inhibitors – paragraph 21.6: replace “benefit is relatively small” with “benefit is small”.

Members noted that the trastuzumab minute from the February 2006 meeting of PTAC should be corrected as follows. Paragraph 20.19 should read

“The Committee noted that adverse cardiac events for each trial were reported separately. In trial B-31 there was an increased rate of severe (NYHA III or IV) heart failure or death at 3 years, of 4.1% in the trastuzumab arm versus 0.8% in the observation arm. In trial N9831, the rate of severe (NYHA III or IV) heart failure or death was 2.9 % in the trastuzumab arm versus 0% in the observational arm. The Committee noted further that the pooled rate of discontinuation in this paper was even higher than in the HERA trial, with 364 (31.4%) patients having discontinued treatment with trastuzumab in the first year, 164 (14.2%) due to asymptomatic decreases in LVEF and 54 (4.7%) due to symptoms of cardiac failure or other adverse cardiac effect). Members also noted that patients taking trastuzumab appeared to have an increase in adverse respiratory side-effects, with four patients in trial B-31 developing interstitial pneumonitis, one of whom died.”

Access criteria for angiotensin-II antagonists

The Committee considered the Special Authority criteria for angiotensin-II antagonists (All antagonists) in response to a number of recommendations from PTAC, its subcommittees and requests from clinicians. In particular, they considered the appropriateness of the current Special Authority criteria with regard to:

- a) Patients with diabetes who are intolerant of ACE inhibitors but have microalbuminuria or proteinuria;
- b) Dual therapy with an ACE inhibitor for patients with diabetes and overt proteinuria who have been unable to be managed with an ACE inhibitor alone; and,
- c) Dual therapy with an ACE inhibitor for patients with hypertension who have been unable to be managed with an ACE inhibitor alone.

Patients with diabetes who are intolerant of ACE inhibitors but have microalbuminuria or proteinuria

The Committee considered that All antagonists should be available for patients with diabetes with microalbuminuria or proteinuria who are intolerant of ACE inhibitors, even though the majority of this group are likely to be currently accessing an All antagonist under the current hypertension criteria.

Dual therapy with an ACE inhibitor for patients with diabetes and overt proteinuria, who have been unable to be managed with an ACE inhibitor alone

The Committee considered that there was reasonable evidence to support dual therapy with an All antagonist and an ACE inhibitor for patients with chronic kidney disease and proteinuria of greater than 1 gram per 24 hours, who have been unable to be managed with an ACE inhibitor alone.

The Committee noted that there were no long-term trials and that there was a lack of survival benefit in All antagonist diabetic trials despite improved renal outcomes. The Committee considered that these limitations were a concern but that any treatment that delays the need for dialysis was potentially worthwhile.

The Committee considered that there were likely to be access issues if dual therapy was limited to specialists only. Therefore, it considered that vocationally registered general practitioners should also be able to apply under the Special Authority criteria.

Dual therapy with an ACE inhibitor for patients with hypertension who have been unable to be managed with an ACE inhibitor alone.

The Committee noted that dual therapy with an ACE inhibitor plus an All antagonist for patients with hypertension, who have been unable to be managed with an ACE inhibitor alone, was previously available.

The Committee considered that the inability to prescribe dual therapy for this patient group could be inconvenient at times and that there was some evidence to support dual therapy in hypertension. However, the Committee considered that dual therapy carries a potentially high fiscal risk, which is difficult to define.

The Committee recommended the following Special Authority criteria for angiotensin-II antagonists:

Initial application (ACE inhibitor intolerance) only from a relevant specialist or general practitioner. Approvals valid without further renewal unless notified for applications meeting the following criteria:

Either:

1 Both:

1.1 Either:

1.1.1 Patient has been treated with, and cannot tolerate an ACE inhibitor, due to persistent cough, and on retrial, or trial of another ACE inhibitor, develops recurrent and persistent cough; or

1.1.2 Patient has experienced angioedema on an ACE inhibitor at any time in the past or has experienced angioedema (even if not using an ACE inhibitor) in the last 2 years; and

1.2 Any of the following:

1.2.1 Patient has congestive heart failure; or

1.2.2 Patient has raised blood pressure that has not been controlled with fully funded beta blockers or diuretics due to contraindication, intolerance or insufficient response despite appropriate dosage; or

1.2.3 Patient has diabetes and microalbuminuria or proteinuria.

Renewal - (Previous approval has expired) only from a relevant specialist or general practitioner. Approvals valid without further renewal unless notified where the treatment remains appropriate and the patient is benefiting from treatment

Initial application (Dual therapy for proteinuria) only from a relevant specialist or vocationally registered general practitioner. Approvals valid without further renewal unless notified for applications meeting the following criteria:

2 The patient has chronic kidney disease and proteinuria of greater than 1 gram per 24 hours and is being treated with the maximum tolerated dose of an ACE inhibitor.

Renewal - (Previous approval has expired) only from a relevant specialist or vocationally registered general practitioner. Approvals valid without further renewal unless notified where the treatment remains appropriate and the patient is benefiting from treatment

The Committee noted that PHARMAC staff estimate that up to 3800 patients could be eligible under criterion 1.2.3 above, and that the Diabetes Subcommittee estimate that only a few hundred patients would be eligible under criterion 2 above. The Committee considered that these patient number estimates were reasonable.

The Committee **recommended** using the above dual therapy (ACE inhibitor plus an All antagonist) Special Authority criteria for patients who have continuing proteinuria greater than 1 gram per 24 hours and are being treated with the maximum tolerated dose of an ACE inhibitor, with a moderate 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*; (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 cost to health service users*.

Clopidogrel

The Committee considered the Special Authority criteria for clopidogrel as a result of feedback from the suppliers, the availability of new evidence regarding the addition of clopidogrel to aspirin and the use of aspirin and esomeprazole instead of clopidogrel in patients with a previous bleed from a peptic ulcer.

The Committee noted that it, and the Cardiovascular Subcommittee, had previously discussed clopidogrel on a number of occasions. It also noted that the Cardiovascular Subcommittee had drafted the original Special Authority criteria.

The Committee noted that the troponin T and troponin I tests have different upper limits of normal. The Committee considered that using 0.03 mcg/L as the cut-off point for the troponin T test was appropriate. However, it was inappropriate for the troponin I test as the levels are defined by the manufacturers. Therefore, the Committee considered that any test result greater than the upper limit of the reference range should be used as the cut-off point.

The Committee noted that the Cardiovascular Subcommittee had not recommended the use of the TIMI score. The Committee considered that the TIMI score should not be included in the Special Authority criteria as it is not used routinely in clinical practice in New Zealand.

The Committee noted that patients could experience thrombotic occlusions of a stent after they had completed the initial course of clopidogrel and continued with aspirin alone. The Committee considered that clopidogrel should be available to patients who, while on treatment with aspirin, experience stent thrombosis after stopping clopidogrel treatment.

The Committee noted that bare metal stents were not commonly used and that the current duration of clopidogrel treatment after insertion of sirolimus-eluting or paclitaxel-eluting stents was six months. The Committee considered that the Special Authority criteria should reflect this.

The Committee noted that the supplier's suggested criteria included patients post-elective stenting, instead of post stenting. The Committee felt that the rationale for this amendment was unclear and sought clarification from the supplier.

The Committee considered the use of clopidogrel for patients who had previous upper gastrointestinal bleeding. The study by Chan et al ("Clopidogrel versus Aspirin and Esomeprazole to prevent recurrent ulcer bleeding", *New Engl J Med* Jan 20, 2005 352;3 238-44) suggests that clopidogrel caused a significantly higher incidence of recurrent ulceration in patients who had fully recovered from previous ulcer bleeds compared to a combination of PPI and aspirin. The Committee also considered that in the CAPRIE study, where there was a direct comparison made between clopidogrel and aspirin, the former was not associated with excess risk of upper GI bleeding. The Committee considered that evidence for use of clopidogrel in patients who had previous GI bleeding due to peptic ulcer disease is inconclusive.

The Committee recommended the following changes to the clopidogrel Special Authority criteria (changes are in bold and strikethrough).

Clopidogrel Special Authority

Special Authority - Retail Pharmacy

1. For patients who, while on treatment with aspirin, experience an acute myocardial infarction, or episode of pain at rest of greater than 20 minutes duration due to coronary disease and requiring admission to hospital for at least 24 hours, or have a troponin T test or troponin I test result greater ~~than or equal to 0.03 mcg/L~~ **than the upper limit of the reference range, or have a previous history of a revascularisation procedure.**
 - Approvals are valid for three months.
 - Reapplications can be made for patients who experience an additional vascular event within two weeks of ending treatment with clopidogrel.
 - Re-approvals are valid without further renewal unless notified.
2. **For patients who, while on treatment with aspirin, experience documented stent thrombosis after stopping clopidogrel.**
 - **Approvals are valid without further renewal unless notified.**
3. For aspirin-intolerant patients (see definition below), following stroke, or transient ischemic attack, or acute myocardial infarction, or episode of pain at rest of greater than 20 minutes duration due to coronary disease and requiring admission to hospital for at least 24 hours, or have a troponin T test or troponin I test result greater ~~than or equal to 0.03 mcg/L~~ **than the upper limit of the reference range.**
 - Approvals are valid without further renewal unless notified.
4. For patients awaiting stenting, coronary artery bypass grafting, or percutaneous coronary angioplasty following acute coronary syndrome.
 - Approvals and re-approvals are valid for six months
5. Post-stenting:
 - 5.1 ~~Bare metal stents~~
 - ~~Approvals are valid for one month.~~
 - 5.2 ~~Sirolimus eluting stents~~
 - ~~Approvals are valid for two months.~~
 - 5.3 ~~Paclitaxel eluting stents~~
 - Approvals are valid for six months.
 - No reapprovals issued (although new applications can be submitted under points 1,2 and 3 above).
6. Applications and re-applications can be made by a relevant Specialist

Notes:

- Intolerance to aspirin is defined as a history of:
 - ~~upper gastrointestinal bleeding; or~~
 - anaphylaxis, urticaria or asthma within four hours of ingestion of aspirin, other salicylates or NSAIDs.

Erlotinib (Tarceva) for Non-Small Cell Lung Cancer

The Committee reviewed an application from Roche Pharmaceuticals for the listing of erlotinib (Tarceva) on the Pharmaceutical Schedule for use in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have previously received chemotherapy.

The Committee noted that the submission centred on a single, well designed, double blind, placebo controlled phase III study, BR.21, which enrolled patients with Stage IIIb or IV NSCLC who had received one or two previous regimens of combination chemotherapy and were not eligible for further chemotherapy. 731 patients were enrolled and randomised 2:1 to receive erlotinib 150mg (n=488) or placebo (n=243). The Committee noted that the median age of patients enrolled was 61 years and that there were more never-smokers in the erlotinib group

(21.3% versus 17.3%), but fewer EGFR-positive patients (24% versus 27.6%); however EGFR status was unknown in greater than 50% of patients.

The Committee noted that the primary endpoint of this study was overall survival, with the analysis planned after 582 deaths had been observed. At data cut off, with a median follow-up of 16 months, 587 deaths had occurred. This study reported median overall survival (OS) of 6.7 months in the erlotinib treated patients compared with 4.7 months for placebo. The one-year survival rate was 31% versus 22% in favour of erlotinib. Progression free survival was 2.2 months in the erlotinib treated patients compared with 1.8 months for placebo.

The Committee noted that erlotinib was associated with an increase in clinically significant adverse effects. The Committee noted that in 19% of patients the erlotinib dose was reduced because of adverse effects, with 5% discontinuing treatment completely. The Committee noted that the most common adverse effects associated with erlotinib treatment were rash (76%, 9% grade 3 to 5), anorexia (69%, 9% grade 3 to 5) and diarrhoea (55%, 6% grade 3 to 5).

The Committee considered that there was an unmet clinical need in patients with advanced NSCLC, for whom the prognosis is poor. However, it considered that erlotinib provided only a modest, two month improvement in median survival compared to placebo and was associated with significant adverse effects.

The Committee noted that comparative trials of erlotinib against other chemotherapy agents in NSCLC had not been conducted and the Committee considered that other chemotherapeutic agents, in particular docetaxel, may have similar therapeutic effects to erlotinib in this population.

The Committee considered that the cost for erlotinib was high relative to the modest clinical benefit and there would be increased costs associated with treatment of adverse events. The Committee considered that the rate and severity of erlotinib adverse effects was unacceptably high for what was essentially palliative treatment.

The Committee **recommended** that the application for funding of erlotinib on the Pharmaceutical Schedule for use in patients with locally advanced or metastatic non-small cell lung cancer be declined.

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 (viii) *The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.*

Trastuzumab (Herceptin) – additional information requested

The Committee noted that it had first reviewed the application from Roche Pharmaceuticals for the listing of trastuzumab (Herceptin) for early HER-2 positive breast cancer at its February 2006 meeting, prior to Medsafe registration. The Committee had requested that further information be provided in relation to any extended benefits and risks and that the Cancer Treatments Subcommittee of PTAC (CaTSoP) review the application.

The Committee noted that CaTSoP had reviewed the application on trastuzumab in April 2006. The Committee noted that: the supplier had provided a cost-utility analysis (CUA) on the use of trastuzumab in early HER-2 positive breast cancer; PHARMAC staff had undertaken a preliminary cost-utility analysis; and that further information had become available on the efficacy and alternative dosing schedules for trastuzumab since the previous meeting, including evidence provided by the supplier.

Minutes of CaTSoP

The Committee agreed with the considerations of the April 2006 meeting of CaTSoP regarding trastuzumab for early HER-2 positive breast cancer.

Further Clinical Information

The Committee considered that the evidence provided in the supplier's addendum to the Submission for trastuzumab did not meet the requirements of their request for information in February 2006.

Members noted that there was no further information supplied on Arm Two (trastuzumab treatment for two years) of the HERA trial (whose interim results for the one-year treatment and observation-only arms were published by Piccart-Gebhart et al N Engl J Med. 2005 Oct 20; 353(16): 1659-72). The Committee considered that these data should soon be available and consideration of these results would be important in any recommendation made.

Members noted that although the supplementary appendix to the Romond et al (N Engl J Med. 2005 Oct 20; 353(16): 1673-84) paper, as posted on the NEJM website, had been provided, the full individual results of the NSABP B-31 and NCCTG N9831 trials had not been provided as requested.

Members noted that the data contained in that appendix for the disease-free survival curves showed similar and statistically significant differences in favour of concurrent trastuzumab therapy, compared to no trastuzumab therapy, in each of the B-31 and N9831 trials. Members noted an early, unpublished analysis of disease-free survival in the N9831 trial supplied in the form of MS PowerPoint slides of a conference presentation (Perez et al. NCCTG N9831: May 2005 update, presentation at the 41st American Society of Clinical Oncology conference, May 2005). Members noted that sequential trastuzumab treatment (Arm B) was not statistically superior to non-trastuzumab treatment (Arm A), but that concurrent trastuzumab treatment (Arm C) resulted in a significant improvement in disease-free survival compared with Arm B. Members considered that although these data were preliminary, they raised concerns about the optimal dosing schedule of trastuzumab treatment. Members noted that slides from an oral presentation do not provide sufficient information to make necessary decisions.

The Committee noted results for the Breast Cancer International Research Group (BCIRG) 006 study (as yet unpublished) supplied in the form of MS PowerPoint slides of a conference presentation (Slamon D., SABCs 2005). It noted that there were three treatment arms: the first containing chemotherapy only, with four cycles of doxorubicin and cyclophosphamide followed by four cycles of docetaxel; the second containing the same chemotherapy regimen plus one year of trastuzumab commenced concurrently with docetaxel; and the third comprising six cycles of docetaxel and carboplatin with one year of trastuzumab commenced concurrently with

the chemotherapy. Members noted that there was a significant improvement in disease-free survival in the trastuzumab treated patients; however, there was no significant difference in disease-free survival between the two trastuzumab arms. There were insufficient data to evaluate overall survival.

The Committee noted the concerns raised by CaTSoP in its consideration of cardiac toxicity associated with trastuzumab. The Committee noted that a pooled data analysis provided by the supplier, including data from HERA, NSABP B-31, NCCTG N9831 and BCIRG 006 trials, indicated that cardiac effects appear to be manageable; however, the long-term impact of these cardiac effects is unknown.

The Committee noted that the rates of cardiac dysfunction appear to be lower when trastuzumab is administered sequentially, rather than concurrently, with chemotherapy. The Committee considered that trastuzumab treatment was associated with higher rates of cardiac toxicity when used with an anthracycline-containing chemotherapy regimen.

The Committee noted the results of a sub-analysis of patients with HER-2 positive breast cancer published as part of the FinHer Study (N Engl J Med. 2006 Feb 23; 354(8): 809-20). The Committee noted that this study had not been provided by the supplier.

The Committee noted that in the FinHer trial, patients were randomized to receive three cycles of either docetaxel or vinorelbine followed by three cycles of fluorouracil, epirubicin and cyclophosphamide. Patients with HER-2 positive breast cancer were further randomised to receive or not receive nine weekly infusions of trastuzumab commenced concurrently with the first cycle of chemotherapy. The Committee noted that, after a median follow-up of 36 months, trastuzumab treatment resulted in a significant improvement in disease-free survival compared with the control group (HR 0.42, p=0.01) without the cardiac toxicity associated with 12 months trastuzumab treatment as reported in other trials.

The Committee noted that the trastuzumab treatment arms of the FinHer trial were relatively small (232 of 1,010 patients) and that the trial might not have been sensitive enough to reliably detect cardiac toxicity. However, the Committee considered that, given the proposed molecular mechanisms of trastuzumab and anthracycline cardiotoxicity, the treatment sequence used in the FinHer study (i.e. trastuzumab prior to anthracycline) might have substantially reduced the risk of developing cardiac toxicity.

The Committee considered that the FinHer Study cast significant doubt over the optimal duration and timing of trastuzumab treatment. Members noted that funding trastuzumab for the proposed indication would have a high budgetary impact, which would have significant consequences for future funding of other pharmaceuticals and services. The uncertainty surrounding the optimal duration and timing of treatment represented a large risk that should be addressed before any decision is made.

General considerations

The Committee considered that it was highly unlikely that the strict entry and exit criteria in clinical trials of trastuzumab would be adhered to in clinical practice. It considered that there might be a higher rate of adverse effects associated with trastuzumab when used in clinical practice due to the likely difficulties in accessing the required cardiac monitoring services.

The Committee considered that the true benefit of trastuzumab in primary breast cancer in relation to its costs lay in the rate of overall survival compared with the duration of treatment. The Committee noted that, at this time, these data are immature.

The Committee considered whether trastuzumab would be used to treat a patient with metastatic breast cancer, if it had already been administered to that patient in the early stages of their breast cancer. The Committee considered that it might be difficult to enforce a restriction on the use of trastuzumab to either primary or metastatic breast cancer. It considered that some physicians would wish to use trastuzumab in both stages of disease if there was a significant time between treatments. The Committee considered that re-treatment with trastuzumab would significantly increase expenditure and was not supported by trial data. The Committee noted that CaTSoP considered that patients should not be re-treated with trastuzumab should the disease recur following treatment for the primary disease.

The Committee reiterated the minute of CaTSoP who considered that, at present, both infusion and echocardiogram services are working at, or near, capacity in DHB hospitals. If trastuzumab were available for early breast cancer, the Committee considered that it may result in increased waiting times for existing cancer treatments and adversely impact on cardiology services.

Cost-Utility Analysis

The Committee reviewed the cost-utility analyses on the use of trastuzumab in the primary setting. The Committee considered that length of relative benefit from trastuzumab would need to be addressed before any further work on other factors such as management of adverse effects was undertaken, to enable an estimate regarding the cost-utility of trastuzumab to be made reliably. The Committee considered that the availability of longer-term data would inform this process.

Recommendation

The Committee concluded that, based on the interim trial results published to date, trastuzumab may have a role in the treatment of primary breast cancer. However, the Committee considered that, with the data provided, they were unable to determine the optimum schedule and duration of trastuzumab treatment, the magnitude of treatment benefit on Overall Survival and, therefore, the cost-effectiveness of trastuzumab.

Given the high cost of trastuzumab, the early nature of the clinical data, and the significant impact on other services and investments in healthcare, which may offer better health outcomes for the money invested, the Committee did not consider it appropriate to make a recommendation for funding this product at this time. It noted that although there was insufficient evidence to make a positive recommendation at this time, it was likely that further data would enable the Committee to address its questions regarding the long-term health benefits, optimal scheduling and cost-effectiveness of trastuzumab.

The Committee noted that it would welcome any substantial body of evidence from the supplier for consideration at subsequent meetings.

Oxaliplatin (Eloxatin) for Colorectal Cancer

The Committee reviewed an application from Sanofi-Aventis for the listing of oxaliplatin (Eloxatin) on the Pharmaceutical Schedule for use in combination with fluorouracil and folinic acid as adjuvant treatment of Stage III (Dukes' C) colon cancer after complete resection of the primary tumour.

The Committee noted that oxaliplatin is currently funded in the Cancer Basket for first-or second-line metastatic colorectal cancer under Special Authority Criteria. The Committee noted that in the adjuvant setting, 5-fluorouracil (5-FU) in combination with leucovorin (LV) for six months is the current standard of care and has increased disease-free survival at five years from 42% to 58% and overall survival from 51% to 64%, when compared with surgery alone.

The Committee noted that the UK National Institute of Clinical Excellence (NICE) recently recommended either oxaliplatin, when used together with 5-FU and LV, or capecitabine monotherapy, as suitable adjuvant treatment for stage III (Dukes' C) colon cancer.

The Committee reviewed data from the pivotal trial (MOSAIC) in which 2246 patients with completely resected stage II or III (60%) colon cancer were randomly assigned to receive 5-FU/LV or FOLFOX4 (oxaliplatin in combination with 5-FU/LV) every two weeks for 12 cycles. The Committee considered that this pivotal study, although open-label, was well designed and will allow for further follow-up.

The Committee noted that this study reported disease free survival (DFS) at three years, the primary endpoint, of 78.2% for FOLFOX and 72.9% for 5-FU/LV, a difference of 5.3%. The Committee noted that for Dukes' C patients the DFS at 3 years was 72.2% versus 65.3% in favour of FOLFOX 4, whereas the difference for Dukes' B patients was not significant.

The Committee reviewed four-year data from the MOSAIC trial available in abstract form. The Committee noted that the DFS was 69.7% versus 61% for Dukes' C patients in favour of FOLFOX 4. Overall survival was 84.3% for FOLFOX 4 versus 82.7% for 5-FU/LV; the Committee noted that this did not achieve statistical significance.

The Committee also noted that a supporting trial, NSABP C-07, with 2492 participants (71% stage III) presented at ASCO 2005 reported a 21% improvement in DFS at three years.

The Committee considered that in the adjuvant setting, a proportion of subjects with DFS at four years would be expected to go into long term remission and therefore overall survival rates for FOLFOX are likely to be better than for 5-FU/LV. The Committee considered that data were available to support the extrapolation of a disease-free survival benefit to an overall survival benefit in colorectal cancer. However, further long-term data are needed to confirm this.

The Committee considered it likely that clinicians would want to use FOLFOX in rectal cancer patients, even though these patients were excluded from the pivotal trial.

The Committee noted that trials of capecitabine with oxaliplatin (CapeOx) are in progress. The Committee considered that CapeOx regimens may be preferred over FOLFOX regimens as they have the advantage of being less resource intensive, requiring fewer IV infusions and less nursing time.

The Committee considered that the addition of oxaliplatin to 5-FU/LV was associated with increased adverse effects, the most common of which were peripheral sensory neuropathy and neutropenia. The Committee considered that, although paresthesia is largely reversible, some patients may have long-term effects.

The Committee considered that the increase in adverse effects would be associated with increased nursing and treatment costs, e.g. administration of G-CSF to neutropenic patients, and monitoring costs e.g. nerve conduction studies.

The Committee **recommended** that oxaliplatin should be funded for adjuvant treatment of patients with Dukes' C colon cancer with medium priority. The Committee considered that access should be restricted to the population enrolled, and the chemotherapy regimen used, in the MOSAIC trial. Applications should be made by a relevant specialist.

The Committee considered that the supplier's Cost-utility Analysis should be reviewed by PHARMAC staff and **recommended** that the application be referred to the Cancer Treatments Subcommittee (CaTSoP) for further advice regarding the targeting criteria and resource implications for DHBs.

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 (viii) *The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.*

Agalsidase beta (Fabrazyme) for Fabry disease

The Committee reviewed an application from Genzyme for the listing of agalsidase beta (Fabrazyme) on the Pharmaceutical Schedule for use in patients with Fabry disease.

The Committee noted that it had previously considered an application for Enzyme Replacement Therapy (ERT) in February 2004. At that time PTAC considered that it would be premature to recommend that ERTs be subsidised in Fabry Disease because of a lack of evidence for long-term treatment benefit.

The Committee considered that the application was of moderate strength and quality. The Committee considered that the application provided good evidence to support the effect of agalsidase beta on the clearance of globotriaosylceramide (GB-3) from plasma and tissue in all age groups and for different ethnicities.

The Committee considered that the application provided either little or no evidence to demonstrate a benefit from agalsidase beta treatment on end-organ function and reduction of clinical progression of Fabry disease. The Committee also considered that there was insufficient evidence to determine optimum dose and dosing protocol including when treatment should be started and who should be treated.

Members had specific concerns about the evidence to support the proposed five-fold greater dose of agalsidase beta compared with agalsidase alpha, as both enzymes have essentially identical effects.

The Committee considered that the lack of good quality long-term evidence suggested that many years of agalsidase beta treatment might be necessary before significant clinical benefits are seen. Members noted evidence that suggested that ERT should be started before the development of proteinuria, LVH or any other organ involvement in order to preserve kidney and cardiac function.

The Committee considered that treatment of advanced Fabry disease with agalsidase beta might not be beneficial.

The Committee noted that current treatment for Fabry disease was aimed at symptomatic management and preserving cardiac and renal function and that it may include organ transplantation.

The Committee considered that there were still concerns around serious adverse effects, infusion-related reactions and antibody formation related to agalsidase beta treatment.

The Committee considered that the non-pharmaceutical costs of agalsidase beta treatment such as infusion cost, nursing and medical costs, diagnostic testing, blood tests, imaging, organ biopsies and costs associated with infusion reactions and adverse effects would be significant. The Committee considered that there may be eventual savings in treatment of end-organ damage, but this benefit is speculative and not supported by evidence.

The Committee considered that listing agalsidase beta would have little impact on alternate pharmaceutical costs.

The Committee **recommended** that the application for the listing of agalsidase beta (Fabrazyme) on the Pharmaceutical Schedule be declined.

The Committee considered that issues around high-cost treatments, such as agalsidase beta, might be addressed by PHARMAC's High Cost Pharmaceuticals Review.

Etanercept (Enbrel) & infliximab (Remicade) for second-line tumour necrosis factor alpha (TNF) inhibitor treatment of Rheumatoid Arthritis

The Committee considered applications from Schering-Plough, the supplier of infliximab (Remicade), and Wyeth, the supplier of etanercept (Enbrel), for the listing of a second-line TNF inhibitor after adalimumab (Humira). The Committee noted that the applications had been made by the suppliers at the behest of PHARMAC staff as a result of responses to consultation by the New Zealand Rheumatology Association (NZRA) and other patient interest groups following the listing of adalimumab on the Pharmaceutical Schedule.

The Committee accepted that there is an unmet clinical need for a second TNF inhibitor to be available for use in patients with rheumatoid arthritis in whom adalimumab has failed, either because of lack of efficacy or because of adverse effects.

The Committee noted that it had reviewed evidence for the use of infliximab and etanercept in rheumatoid arthritis on numerous occasions. It noted that the evidence provided in the current application was specific to the respective use of either infliximab or etanercept as a second-line

TNF agent. The Committee considered that both applications were of medium quality and that much of the information was duplicated in the applications.

The Committee considered that the evidence provided in the applications was not strong, but highlighted a growing body of evidence to support the use of a second-line TNF inhibitor in rheumatoid arthritis. It noted that, while there is evidence that a second TNF inhibitor can be effective where a first has failed, there was little evidence to inform a choice about which agent to use, or how to sequence the different therapies.

In addition, the Committee noted a newsletter from the British Society of Rheumatology Biologics Register provided by the NZRA. The Committee noted the newsletter reported registry data of outcomes for 6,138 patients who had received treatment with one or more TNF inhibitor agents. The Committee noted that the registry data were in effect a non-randomised, uncontrolled and unblinded cohort study, but considered that they were currently the best evidence available.

The Committee considered that the new evidence indicated that if a patient had ceased treatment with a TNF inhibitor due to ineffectiveness or adverse effects, the expected benefit upon trial of a second-line agent would be 70%-80% of that expected for any patient receiving a TNF inhibitor for the first time. Expected benefit was higher for patients stopping the first TNF inhibitor for adverse effects than for those stopping for lack of efficacy. The Committee noted that there did not seem to be any serious safety concerns about exposing patients to a second TNF inhibitor, although adverse effects were more likely in those who stopped the first TNF inhibitor for adverse effects.

The Committee noted that infliximab was a hospital-administered product and that it was not practically possible for it to be used in a community setting. It further noted that any use of infliximab would be at the discretion of an individual hospital and that PHARMAC could not restrict its use.

The Committee **recommended** that the application to list infliximab (Remicade) on the Pharmaceutical Schedule be declined.

The Committee noted that etanercept was already listed on the Pharmaceutical Schedule for the treatment of Juvenile Idiopathic Arthritis (JIA). The Committee noted that etanercept was a drug that could easily be administered in a community setting. The Committee noted that etanercept has a different mode of action to adalimumab.

The Committee **recommended** that etanercept be listed on the Pharmaceutical Schedule as a second-line agent to adalimumab with a moderate priority.

Imiquimod (Aldara) for Superficial Basal Cell Carcinoma

The Committee considered an application from 3M Pharmaceuticals for the listing of imiquimod on the Pharmaceutical Schedule for use in patients with superficial basal cell carcinoma.

The Committee noted that PTAC had previously considered imiquimod for the treatment for genital warts but that, to date, a listing in the Pharmaceutical Schedule has not occurred.

The Committee noted that basal cell carcinoma is a disease that predominantly occurs in Caucasians and that basal cell carcinoma is likely to become more prevalent in the aging population.

The Committee noted that there are other therapies for superficial basal cell carcinoma, including standard surgical excision, curettage and cautery, MOH's micrographic excision, radiation therapy, cryotherapy, 5-FU (Efudix), PDT (Metfix), intralesional interferon alpha and oral retinoids.

The Committee considered that surgery is the preferred treatment and that it should be the comparator for other treatment options. However, the Committee acknowledged that access to publicly funded surgical clinics may vary in different parts of the country and that surgery may not be appropriate for some patients, either due to the anaesthetic risk or for cosmetic reasons. If surgery is not appropriate then the Committee considered that radiation therapy should be the clinical comparator.

The Committee noted the results of a 2006 Cochrane review, which showed that imiquimod could be a potentially useful treatment with a histological clearance rate of 87-88% using once-daily treatments for six weeks.

The Committee considered that the appropriate clinical use for imiquimod would be basal cell carcinomas that are difficult to treat surgically, not the small basal cell carcinomas (less than 2 cm in diameter) that are predominantly used in studies.

The Committee considered that general practitioners perform superficial basal cell carcinoma surgery themselves. However, the Committee considered that imiquimod could have a place in treatment, especially for basal cell carcinomas on the face, for difficult lesions where access to hospital surgery is not available, or for patients who do not desire plastic surgery.

The Committee considered that imiquimod could replace 5-FU for treatment of basal cell carcinomas. Members noted that 5-FU can lead to scarring.

The Committee considered that imiquimod could be appropriate as a second-line treatment after surgery for appropriate cases. These could include the elderly and those who cannot access a dermatologist.

The Committee considered that it would be difficult to have imiquimod available for basal cell carcinoma and not for genital warts.

The Committee considered that there were several concerns with the lack of evidence provided in the application relating to head to head trials with 5-FU, the response of tumours greater than 2 cm in diameter, the durability of the effect of imiquimod, possible wastage of the sachets and the proposed Special Authority criteria.

The Committee requested that some sachets be obtained from the supplier so that it could examine the product and confirm that one sachet would be sufficient to cover the lesion(s) in the vast majority of patients.

The Committee noted the proposed Special Authority criteria. The Committee considered that any Special Authority for a subsidy should include the requirement for a biopsy.

The Committee requested that specialist opinion is sought from general practitioners and dermatologists regarding the Special Authority criteria, the position of imiquimod in therapy, how listing imiquimod in the Pharmaceutical Schedule would impact on 5-FU and if 5-FU should be derestricted if imiquimod was unrestricted.

The Committee considered that specialist surgery should be used as a cost offset in any financial analysis and that compared to this, imiquimod would be more cost effective.

The Committee **recommended** that imiquimod be listed on the Pharmaceutical Schedule with a medium priority, subsequent to the Special Authority criteria being finalised.

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;* (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 cost to health service users.*

Telmisartan (Micardis) for Hypertension

The Committee considered an application from Boehringer Ingelheim for the listing of telmisartan on the Pharmaceutical Schedule as an angiotensin II antagonist for use in the treatment of hypertension.

The Committee considered that telmisartan was another angiotensin II antagonist and that it is as effective as the angiotensin II antagonists currently listed in Section B of the Pharmaceutical Schedule, these being candesartan and losartan.

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

The Committee noted that telmisartan has fewer indications than either candesartan or losartan.

The Committee noted that telmisartan had a longer half-life than other angiotensin II antagonists. Although the Committee noted that there were few head to head studies, it considered that this might be a slight advantage for telmisartan over other angiotensin II antagonists.

The Committee considered that losartan, candesartan and telmisartan could be reference priced for hypertension.

The Committee **recommended** that telmisartan be listed on the Pharmaceutical Schedule, but only if it is cost neutral to the Pharmaceutical Budget.

The Decision Criteria relevant to this recommendation are: (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.*

Buprenorphine/Naloxone (Suboxone) – review of supplier CUA

The Committee considered a cost-utility analysis (CUA) provided by PHARMAC staff on Suboxone (buprenorphine/naloxone) for opiate dependence. The Committee noted that Reckitt Benckiser had provided a CUA that was considered by the Committee at its February 2006 meeting. The Committee noted that PHARMAC staff had since reviewed this CUA and made a number of amendments.

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The Committee considered that the two potential uses of Suboxone, detoxification and maintenance therapy, should be treated as separate indications. The Committee considered that there was a place for Suboxone in maintenance therapy for patients who cannot tolerate methadone.

The Committee noted that there was evidence suggesting that higher doses of Suboxone are more effective and that PHARMAC's CUA was based on a dose of 16 mg per day (compared to 10 mg per day in the supplier analysis). The Committee considered that the dose of Suboxone is likely to be higher than 10 mg per day, most likely between 14-16 mg per day. The Committee **recommended** that a sensitivity analysis be undertaken on the dose of Suboxone.

The Committee noted that amendments had been made to the dispensing regimen of Suboxone in the PHARMAC analysis. The Committee considered that these amendments were appropriate.

The Committee noted that the PHARMAC CUA did not include pharmacist costs for monitoring patients when administering Suboxone. The Committee considered that this cost may be significant and would increase the cost per QALY of Suboxone.

The Committee noted that the supplier analysis had not considered the cost-effectiveness of Suboxone for second-line treatment in patients who cannot tolerate methadone. The Committee noted that the cost per QALY was lower [] if targeted to these patients. The Committee also noted that there could be significant savings to other government sectors, including Justice and Social Development, from funding Suboxone for this group of patients.

The Committee noted that there is no "takeaway" policy in New Zealand for Suboxone and that there are problems (including deaths) associated with the illicit use of methadone in New Zealand. The Committee considered that deaths from opiate overdose might be reduced if Suboxone was available as an alternative to methadone.

The Committee **recommended** that the application be reviewed by the Mental Health Subcommittee and that the subcommittee provide further advice on appropriate Special Authority criteria. The Committee considered that it would be helpful for an addiction specialist to be present during this meeting.

The Committee **recommended** listing Suboxone in the Pharmaceutical Schedule as a detoxification agent and as maintenance therapy in patients who cannot tolerate methadone, and gave a low priority to this recommendation for both indications.

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 (viii) *The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere*.

Note: Portions of this minute are withheld where the making available of that information would be likely to unreasonably prejudice the commercial position of the person who supplied or who is the subject of the information (pursuant to section 9(2)(b)(ii) of the Official Information Act 1982).

Verteporfin (Visudyne)

The Committee considered the response of the supplier to the Ophthalmology Sub-Committee minutes and an audit by [] of patients that she had treated from September 1999 to May 2005 using Photodynamic Therapy and verteporfin in the treatment of choroidal neovascularisation due to age-related macular degeneration and other causes.

The Committee noted that verteporfin had been considered by PTAC twice previously and that the Ophthalmology Subcommittee had also considered it.

The Committee noted that therapy with verteporfin requires appropriate laser equipment and therefore would only occur in hospital outpatient clinics or in the private setting. The Committee considered that use in outpatient clinics could be funded by District Health Boards.

The Committee noted the audit performed by []. The Committee considered that her results were consistent with the findings of the randomised controlled trials and that the treatment of choroidal neovascularisation with verteporfin and photodynamic therapy provided some benefit in terms of reducing the risk of visual loss.

The Committee noted that alternative therapies such as bevacizumab (Avastin) and ranibizumab (Lucentis), which are not used in conjunction with laser equipment, were becoming available and were likely to replace photodynamic therapy for the treatment of choroidal neovascularisation.

The Committee **recommended** that the application be declined as it considered that the Community Pharmaceuticals Budget was not the appropriate funding mechanism for therapies that would only occur in outpatient clinics or private practices.

Note: Portions of this minute have been withheld to protect the privacy of natural persons (pursuant to section 9(2)(a) of the Official Information Act 1982)