Cancer Treatments Subcommittee of PTAC (CaTSoP) meeting

held 5 February 2009

(minutes for web publishing)

The CaTSoP Subcommittee minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2008*:

Note that this document is not necessarily a complete record of the CaTSoP meeting; only the Minutes relating to CaTSoP discussions about an application that contain a recommendation in relation to an application are published.

The CaTSoP Subcommittee may:

(a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or
(c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

Contents

1 Pegfilgrastim

1.1 The Subcommittee considered an application from Roche for the listing of pegfilgrastim on the Discretionary Community Supply (DCS) list.

1.2 Members noted that clinicians are very experienced in the use of filgrastim for neutropenia, with most clinicians using it regularly.

1.3 The Subcommittee noted that the pegylation of filgrastim significantly increases its half-life.

1.4 Members noted that while filgrastim has a half life of approximately 3 hours, the pegylated form has a half life of around 33 hours, although the clearance of pegfilgrastim has a non-linear relationship to dose.

1.5 The Subcommittee noted that the application suggested that filgrastim was administered as ten doses, and that this would be replaced by a single dose of pegfilgrastim.

1.6 Members noted that while ten doses of filgrastim is recommended by the manufacturer for prophylaxis of post chemotherapy neutropenia, based on comparison of this amount versus lesser amounts with respect to likelihood of onset of neutropenic sepsis, they were aware that fewer doses are often used in New Zealand for this purpose and that treatment is often started later than recommended. Members noted that while outpatients typically receive closer to a full ten-dose course, in-patients would be more likely to receive fewer doses, if they recovered faster. The Subcommittee noted that when compared with a ten-dose course of filgrastim, pegfilgrastim had a similar effect on neutrophil count, and resulted in a greater reduction in presentation of patients with febrile neutropenia. The Subcommittee noted that PHARMAC had previously estimated the cost of treating febrile neutropenia at $4,500 per case, which the Subcommittee considered was low.

1.7 The Subcommittee considered that the availability of pegfilgrastim would likely increase the use of granulocyte colony-stimulating factor (G-CSF) treatment.

1.8 Members noted that pegfilgrastim would be particularly useful for out-of-town patients, and would reduce the requirement for District Nurses to administer G-CSF treatment to patients that have difficulty with self-administration.

1.9 The Subcommittee noted that pegfilgrastim appears to be well tolerated.

1.10 Members noted that a DCS listing would enable each DHB to determine which patients would receive filgrastim or pegfilgrastim, and that filgrastim would likely remain the preferred option for in-patient care.

1.11 The Subcommittee considered that pegfilgrastim should not be made available through a Section B listing given that its use is intrinsically linked to chemotherapy provided by DHB Hospitals.

1.12 The Subcommittee **recommended** that pegfilgrastim be listed in the DCS list. The Subcommittee considered that, within the context of cancer treatments, this recommendation should be considered a high priority.

1.13 The relevant decision criteria are: *1: the health needs of all eligible people within New Zealand; 2: the particular health needs of Maori and Pacific peoples; 3: the availability and suitability of existing medicines, therapeutic medical devices and related products and related things; 4: the clinical benefits and risks of pharmaceuticals; 5: the cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; 6: the budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule; and 8: 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).*

2 Erlotinib

2.1 The Subcommittee considered an application from Roche Products for the listing of erlotinib for the second-line treatment of locally-advanced or metastatic non-small cell lung cancer (NSCLC). Members noted that this application had previously been reviewed by PTAC in 2006, at which time it was recommended for decline.

2.2 The Subcommittee noted that platinum doublets are considered the best first-line treatment option for advanced NSCLC, and that docetaxel is commonly used as a second-line agent.

2.3 Members reviewed the results of a clinical study authored by Shepherd et al (N Engl J Med. 2005 Jul 14;353(2):123-32.), which indicated a survival advantage of erlotinib over best supportive care in this patient group. However, the Subcommittee noted that there are no clinical trials that directly compare erlotinib with docetaxel in this patient group.

2.4 The Subcommittee considered that while there is insufficient evidence to indicate that erlotinib is more, or even similarly, effective than docetaxel, it appears that erlotinib may be better tolerated than docetaxel, in particular with regards to development of neutropenia and febrile neutropenia.

2.5 Members noted that not all patients currently receive docetaxel due to its toxicity, and that some patients who do receive it are given fewer than six cycles. Members considered that it was unlikely that the use of erlotinib would significantly reduce expenditure on docetaxel because many patients who

received erlotinib as a second-line agent would likely end up taking docetaxel as a third-line agent upon disease progression.

2.6 Members noted that shifting docetaxel to third-line use may result in an increased number of patients being unable to tolerate docetaxel and, as such, some clinicians may prefer to use erlotinib only after failure of docetaxel.

2.7 The Subcommittee noted that only a small number of patients appear to respond to erlotinib, but that response in those patients, when it occurred, was significant. Members considered that early response is likely to be a good indicator of success.

2.8 The Subcommittee noted that it would be very difficult to target patients that are most likely to benefit from treatment with erlotinib based on the current evidence; however members considered that it would be reasonable to require a renewal application after 3 months with the requirement to demonstrate a lack of disease progression.

2.9 The Subcommittee **recommended** that erlotinib be listed as a second-line treatment for advanced or metastatic NSCLC subject to the above restriction. The Subcommittee considered that, within the context of cancer treatments, this recommendation should be considered a high priority.

2.10 The relevant decision criteria are: *1: the health needs of all eligible people within New Zealand; 2: the particular health needs of Maori and Pacific peoples; 3: the availability and suitability of existing medicines, therapeutic medical devices and related products and related things; 4: the clinical benefits and risks of pharmaceuticals; and 8: 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).*

3 Gefitinib

3.1 The Subcommittee considered an application from AstraZeneca for the listing of gefitinib for the second-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC).

3.2 Members noted that gefitinib had been considered by CaTSoP in 2004, at which time it was recommended for decline.

3.3 The Subcommittee noted that platinum doublets are considered the best first-line treatment option for advanced NSCLC, and that docetaxel is commonly used as a second-line agent.

3.4 The Subcommittee noted that gefitinib is not currently registered for use as a second-line treatment of NSCLC, but is registered for use as a third-line treatment.

3.5 The Subcommittee considered that the evidence supporting the use of gefitinib in the treatment of locally advanced or metastatic NSCLC is inconclusive at present. Members noted that while the INTEREST study (Lancet. 2008 Nov 22;372(9652):1809-18.) indicated a benefit of gefitinib over docetaxel as a second-line treatment of NSCLC in this patient group, in other studies gefitinib has failed to prove non-inferiority to docetaxel (J Clin Oncol. 2008 Sep 10;26(26):4244-52.) or an advantage over placebo (Lancet. 2005 Oct 29-Nov 4;366(9496):1527-37; J Clin Oncol. 2008 May 20;26(15):2450-6.).

3.6 Members considered that the side-effect profile of gefitinib appears to be better than docetaxel, particularly with regards to neutropenia.

3.7 The Subcommittee **recommended** declining the application to list gefitinib, on the basis of lack of evidence of efficacy.

3.8 The relevant decision criterion is: *4: the clinical benefits and risks of pharmaceuticals.*

4 Sunitinib

4.1 The Subcommittee considered an application from Pfizer for the listing of sunitinib for the treatment of advanced renal cell carcinoma (RCC).

4.2 Members noted that PTAC and CaTSoP had previously reviewed this application in 2007, at which time it was recommended for decline. Members noted that this revised application had been referred to the Subcommittee by PTAC.

4.3 The Subcommittee noted that the current treatment for advanced RCC is interferon alpha; however, members noted that interferon alpha has a poor tolerability profile and that many patients are not administered this product as a result.

4.4 The Subcommittee noted that it had previously reviewed the results of a study reported in 2007 by Motzer et al (N Engl J Med. 2007 Jan 11;356(2):115-24) that compared sunitinib with interferon alpha in patients with advanced RCC. Members noted that the results reported at the time showed that sunitinib provided a six month increase in progression-free survival compared with interferon alpha.

4.5 The Subcommittee noted that the updated, unpublished, data provided by Pfizer (presented at the American Society of Clinical Oncology last year) showed that the progression-free survival benefit was preserved and that there was a 4.6 month increase in median overall survival. Members noted that while the increase in overall survival was not statistically significant (p=0.051), crossover between trial arms had likely confounded the results.

4.6 Members noted that the quality of life appeared to be improved with sunitinib.

4.7 The Subcommittee considered that there appeared to be little basis, other than the entry criteria in the Motzer paper, upon which to prospectively target patients that would be most likely to benefit from sunitinib, and similarly, it would be difficult to target continued treatment based on early response.

4.8 The Subcommittee reiterated its previous view that sunitinib is, essentially, a very high-cost palliative treatment and **recommended** that the application to list sunitinib be declined.

4.9 The relevant decision criteria are: *1: the health needs of all eligible people within New Zealand and 6: the budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

5 Bortezomib

5.1 The Subcommittee considered an application from Janssen-Cilag for the listing of bortezomib for the second-line treatment of multiple myeloma.

5.2 Members noted that PTAC and CaTSoP had previously considered bortezomib as a third-line agent for multiple myeloma, at which time the application was recommended for decline. Members noted that the current application had been referred to the Subcommittee by PTAC.

5.3 The Subcommittee noted that, in New Zealand, patients with multiple myeloma aged under 65 years and otherwise healthy patients with multiple myeloma aged over 65 years typically receive chemotherapy (e.g. cyclophosphamide and dexamethasone) followed by transplant. Other patients generally receive prednisone and melphalan, followed by thalidomide upon relapse. Members noted that thalidomide is typically administered in New Zealand at a dose of 100 mg per day and is frequently used in conjunction with steroids (often dexamethasone) and sometimes with oral chemotherapy (e.g. cyclophosphamide).

5.4 Members noted that thalidomide is an oral preparation, whereas bortezomib requires intravenous injection. The Subcommittee noted that there are no head-to-head studies comparing bortezomib with thalidomide.

5.5 The Subcommittee noted the results of the APEX study (N Engl J Med. 2005 Jun 16;352(24):2487-98) and the APEX follow-up data (Blood. 2007 Nov 15;110(10):3557-60). Members noted that after a median follow-up of 22 months, overall survival increased by 6 months with bortezomib compared with dexamethasone.

5.6 The Subcommittee noted that crossover was allowed in the APEX study, and that 62% of patients in the dexamethasone arm eventually switched to bortezomib. Members noted that such crossover made the overall survival data difficult to interpret.

5.7 Members considered that bortezomib should be used in combination with dexamethasone, which appears to increase the rate of response.

5.8 The Subcommittee noted that patients would probably receive 5 or 6 cycles of bortezomib on average, with up to 8–11 cycles given to responding patients; however members considered that access should be limited to 4 cycles for patients who do not demonstrate an early response.

5.9 The Subcommittee noted the results of the Vista study (the addition of bortezomib to prednisone and melphalan in treatment-naïve patients with multiple myeloma), which indicated that bortezomib may have a role in the first-line setting. However, members noted that this use would be outside of the current indication.

5.10 The Subcommittee considered that the use of bortezomib as a second-line agent for multiple myeloma would not replace thalidomide, but would instead result in thalidomide becoming a third-line agent.

5.11 The Subcommittee **recommended** that bortezomib be listed as a second-line agent for multiple myeloma. The Subcommittee recommended that initial applications be valid for three months, with the requirement for a partial response to be demonstrated after four cycles for further approval to be granted.

5.12 The Subcommittee considered that, within the context of cancer treatments, this recommendation should be given a medium-to-high priority.

5.13 The relevant decision criteria are: 1: *the health needs of all eligible people within New Zealand; 4: the clinical benefits and risks of pharmaceuticals; and 8: 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).*

6 Gemcitabine

6.1 The Subcommittee considered an application from the New Zealand Association of Cancer Specialists to widen access to gemcitabine to allow for its use as adjuvant treatment of macroscopically resected pancreatic cancer.

6.2 Members considered that the application was helpfully succinct, with good supporting evidence.

6.3 The Subcommittee noted that a small proportion of pancreatic cancers are resectable, and that 5-fluorouracil is currently the standard adjuvant treatment for resectable disease. Members noted that the evidence for the use of 5-fluorouracil is considered controversial.

6.4 The Subcommittee reviewed a study by Oettle et al (JAMA. 2007 Jan 17;297(3):267-77) which compared gemcitabine with observation in 354 patients with resected pancreatic cancer. Members noted that in this study, gemcitabine was associated with a significant increase in disease-free survival of 6.5 months.

Members also noted a small, but non-significant, increase in overall survival of 1.9 months.

6.5 Members noted that patients with advanced pancreatic cancer are currently able to be treated with funded gemcitabine. Members noted that if access to re-treatment with gemcitabine was restricted in patients with advanced pancreatic cancer who had previously received gemcitabine as adjuvant treatment, the overall cost of this application would be relatively low in the longer term.

6.6 The Subcommittee **recommended** that the Special Authority restriction applying to gemcitabine be amended to allow for the adjuvant treatment of macroscopically resected pancreatic cancer.

6.7 The Subcommittee also **recommended** that the Special Authority restriction applying to metastatic pancreatic cancer be amended to prevent re-treatment with gemcitabine if disease progression occurs within 12 months of adjuvant treatment.

6.8 The Subcommittee considered that, within the context of cancer treatments, these recommendations should be considered a high priority.

6.9 The relevant decision criteria are: 1: *the health needs of all eligible people within New Zealand; 3: the availability and suitability of existing medicines, therapeutic medical devices and related products and related things; 4: the clinical benefits and risks of pharmaceuticals; 5: the cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; and 8: 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)*.

7 Alemtuzumab

7.1 The Subcommittee considered a paper from PHARMAC staff on alemtuzumab for the third-line treatment of chronic lymphocytic leukaemia (CLL).

7.2 The Subcommittee noted that PTAC and CaTSOP had previously considered an application from Bayer New Zealand Ltd for the listing of alemtuzumab on the Pharmaceutical Schedule. The Subcommittee noted that CaTSOP had recommended funding alemtuzumab with a medium priority for patients with CLL who are to have an allogeneic transplant but are intolerant to fludarabine, and patients with 17p53 deletion refractory to fludarabine treatment.

7.3 Members noted that the reasons the Subcommittee had recommended restricting access to only these patient groups included the limited efficacy data; the high risk of side effects high cost of treatment; high resource requirements to administer the drug and associated prophylaxis treatments.

7.4 The Subcommittee noted that PHARMAC staff had provided several case-control studies examining the effectiveness of alemtuzumab when used in the

conditioning regimen prior to transplantation and when targeted to patients with 17p53 deletion (Blood. 2006 Feb 15;107(4):1724-30; Leuk Lymphoma. 2004 Dec;45(12):2455-8; Blood. 2004 May 1;103(9):3278-81; Haematologica. 2005 Oct;90(10):1435-6), which the Subcommittee considered to be level 3 evidence.

7.5 The Subcommittee noted that the case-control studies indicated that an alemtuzumab- based regimen was feasible and effective when targeted to these subgroups of patients, and may potentially be curative in a small number of patients.

7.6 The Subcommittee noted that patients administered alemtuzumab had a higher risk of infections and that approximately 20% of patients die of infection-related complications.

7.7 The Subcommittee considered that there would be 1–2 patients per year in New Zealand who would meet the proposed targeting criteria for alemtuzumab. It was noted that there had been one application under CaEC in 2008.

7.8 The Committee recommended that alemtuzumab not be listed in the Pharmaceutical Schedule, but should instead be managed through Cancer Exceptional Circumstances.