

Cancer Treatments Subcommittee of PTAC meeting held 26 August

2011

(minutes for web publishing)

Cancer Treatments 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 Cancer Treatments Subcommittee meeting; only the relevant portions of the minutes relating to Cancer Treatments Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

The Cancer Treatments 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.

These Subcommittee minutes were reviewed by PTAC at its meeting on 10 & 11 November 2011, the record of which will be available in January 2012.

Contents

1	Matters Arising	3
2	Therapeutic Group Review	4
3	Rituximab for maintenance therapy in relapsed/refractory follicular lymphoma	6
4	Filgrastim.....	8
5	Review of Special Authorities.....	9

1 Matters Arising

1.1. *Trastuzumab for gastric cancer*

- 1.1.1. The Subcommittee noted a letter from Roche products NZ Limited, dated 28 June 2011, regarding its April 2011 minute and recommendations for the funding of trastuzumab for HER 2 positive locally advanced or metastatic gastric cancer.
- 1.1.2. The Subcommittee noted that in making its recommendations it was appropriate to consider the absolute benefits of trastuzumab in gastric cancer, rather than its relative benefits compared with trastuzumab for HER 2 positive breast cancer.
- 1.1.3. The Subcommittee requested that PHARMAC staff respond to Roche thanking it for the letter; however, members did not consider that the points raised substantially changed their views on the evidence. The Subcommittee endorsed its April 2011 minute and reiterated its **recommendation** that the application for trastuzumab for HER 2 positive locally advanced or metastatic gastric cancer be declined.
- 1.1.4. The Subcommittee noted that it would be happy to reconsider the funding of trastuzumab for gastric cancer when further confirmatory clinical trial evidence became available.

1.2. *Oral Cyclophosphamide discontinuation*

- 1.2.1. The Subcommittee noted that Pfizer had notified PHARMAC that it is discontinuing global production of cyclophosphamide (Cyclobastin) 50 mg tablets.
- 1.2.2. The Subcommittee considered that continued supply of cyclophosphamide tablets was essential. Members noted that although most oral cyclophosphamide was used in non-oncology settings, it is a key component of some multiple myeloma treatment regimens and was occasionally used in ovarian and breast cancer and chronic lymphocytic leukaemia (CLL) patients.
- 1.2.3. The Subcommittee **recommended** that PHARMAC staff seek an alternative supplier for cyclophosphamide tablets. Members considered that either a 50 mg or 100 mg tablet strength would be acceptable. Members noted that if only a 100 mg tablet was available, it needed to be scored to enable dosing in 50mg increments.

1.3. *Erlotinib and EGFr testing*

- 1.3.1. The Subcommittee noted an e-mail from [withheld under the Official Information Act 1982, section 9(2)(a)] requesting that funding for erlotinib be widened to include first line treatment of patients with advanced non small cell lung cancer (NSCLC) with documented evidence of EGFr activating mutations. Members noted that since erlotinib was funded for second line treatment of patients with advanced NSCLC, uptake over the first few months was considerably higher than anticipated.

Members considered that this represented a backlog of patients and growth was not likely to continue to increase at the same rate.

- 1.3.2. The Subcommittee noted that since erlotinib was funded, new evidence from the European Erlotinib Versus Chemotherapy (EURTAC) study was presented at ACSO 2011 (Rosell et al J Clin Oncol 29: 2011 (suppl; abstr 7503)) which indicated it should be targeted to patients with NSCLC EGFr activating mutations. However, the Subcommittee did not consider it had sufficient information at this time to make any recommendations regarding changes to the funding of erlotinib.
- 1.3.3. The Subcommittee **recommended** that PHARMAC staff write to [withheld under the Official Information Act 1982, section 9(2)(a)], thanking him for his e-mail, and requesting that he, and/or Roche, submit a funding application including data from the EURTAC study.[Withheld under the Official Information Act 1982, section 9(2)(b)(ii)].

1.4. *Nilotinib and imatinib proposal*

- 1.4.1. The Subcommittee noted further information from PHARMAC staff regarding PHARMAC's February 2011 consultation on a proposal to fund nilotinib for CML and widen funded access to imatinib. Members noted that the proposal was on hold and PHARMAC had yet to secure an agreement with Novartis that would see nilotinib funded. [Withheld under the Official Information Act 1982, section 9(2)(b)(ii)]
- 1.4.2. The Subcommittee considered that if nilotinib was listed for any CML patient, the majority of new patients would be started on dasatinib or nilotinib, with the market share for imatinib decreasing over time. However, members considered that some haematologists would still preferentially use imatinib unless more compelling data, such as overall survival benefit for nilotinib and dasatinib compared with imatinib, became available.
- 1.4.3. The Subcommittee considered that nilotinib would be preferred over dasatinib for patients with mutations predicting greater response to nilotinib compared with dasatinib and patients with pre-existing fluid retention or effusions that may worsen on dasatinib.
- 1.4.4. The Subcommittee considered that if PHARMAC was unable to secure an agreement with Novartis that would enable nilotinib to be funded for any CML patient it would be useful to have it funded as a 3rd line option. Under these circumstances, the Subcommittee **recommended** nilotinib be funded for patients who are intolerant to, or who have CML disease resistant to both imatinib and dasatinib or with known mutations predicting inferior response to imatinib and dasatinib. Members considered that this would be a very small market.

2 Therapeutic Group Review

2.1 *Thalidomide for myelofibrosis*

- 2.1.1 The Subcommittee noted that PHARMAC had recently received two cancer exceptional circumstances (CaEC) applications for the funding of thalidomide for myelofibrosis. Members also noted that prior to these two recent applications PHARMAC had received 3 previous applications which were considered under the Hospital Exceptional Circumstances Scheme. Members noted that applicants had argued that the funding of thalidomide for myelofibrosis would be cost saving to DHBs because in some patients it may reduce, or even eliminate, the need for blood transfusions.
- 2.1.2 The Subcommittee reviewed evidence for the use of thalidomide in this setting from a phase II dose escalation study (Marchetti et al 2004 J Clin Oncol 22:424-431) and a review article (Hoffman and Rondelli Hematology Am Soc Hematol Educ Program. 2007:346-54.)
- 2.1.3 The Subcommittee considered that myelofibrosis was a rare disease and treatment was aimed at supportive care and controlling disease symptoms such as splenomegaly and cytopaenia. Members considered that there were several funded options, such as oral chemotherapy including hydroxyurea and thioguanine.
- 2.1.4 The Subcommittee considered that the evidence for use of thalidomide in this setting was weak and limited to small case studies. Members noted that in the Marchetti study, 63 patients were treated with thalidomide starting at 50mg daily and increasing to 400mg daily as tolerated. Members noted that of the 18 transfusion dependent patients enrolled, 9 patients (50%) had a reduction in blood transfusion requirement and 7 patients (39%) achieved transfusion independence. However, members considered that the difference in spleen size was not clinically significant and half the patients discontinued thalidomide by six months in this study.
- 2.1.5 The Subcommittee considered that the funding of thalidomide for patients with myelofibrosis was of limited efficacy and **recommended** that applications through Exceptional Circumstances or the Pharmaceutical Schedule should be declined.

2.2 *Lenalidomide for del(5q) myelodysplastic syndromes*

- 2.2.1 The Subcommittee noted that PHARMAC had received 4 CaEC applications in the last 2 years for the funding of lenalidomide for patients with del(5q) myelodysplastic syndrome.
- 2.2.2 The Subcommittee considered that the number of patients presenting with del(5q) myelodysplastic syndrome was small. Members considered that there was sufficient evidence to suggest lenalidomide was a standard treatment option in such patients; therefore, such funding should not, in general, be considered under the CaEC scheme unless there were some other factors which made an individual's specific situation rare or unusual.
- 2.2.3 The Subcommittee considered that it would be appropriate for PHARMAC to consider a Pharmaceutical Schedule funding application for lenalidomide for patients with del(5q) myelodysplastic syndrome. The Subcommittee

recommended that PHARMAC staff request a funding application from the supplier.

2.3 *Sunitinib for Imatinib refractory GIST*

2.3.1 The Subcommittee noted that PHARMAC had received 2 applications under CaEC for the funding of sunitinib for patients with imatinib refractory advanced Gastro-Intestinal Stromal Tumours (GIST). Members noted that both applications had been declined because PTAC had considered funding of sunitinib in this setting in February 2007 and recommended it be declined. Members noted that the evidence provided with the CaEC applications was reviewed by PTAC when it made its decline application, and members were not aware of any significant new evidence.

2.3.2 The Subcommittee noted that Novartis had recently closed recruitment into its nilotinib for GIST compassionate supply program; therefore, PHARMAC will likely see more applications for the funding of sunitinib for imatinib refractory GIST.

2.3.3 The Subcommittee considered that in the absence of new data, the passage of time since PTAC's decline recommendation was made was not relevant. Members considered that PTAC's 2006 recommendation remained valid given the current evidence and **recommended** that CaEC be declined.

2.3.4 The Subcommittee **recommended** that PHARMAC invite the supplier, or clinicians, to resubmit a funding application should any new, relevant, data become available

3 **Rituximab for maintenance therapy in relapsed/refractory follicular lymphoma**

3.1 The Subcommittee considered an application from Roche Products (NZ) Ltd for funding of rituximab (MabThera) on the Pharmaceutical Schedule to be widened to include maintenance treatment in patients with relapsed/refractory follicular Non-Hodgkin's Lymphoma (NHL).

3.2 The Subcommittee noted that the application had been reviewed by PTAC at its May 2011 meeting where it recommended that the application be deferred pending longer term data from relevant studies becoming available.

3.3 The Subcommittee noted that evidence from five studies in the relapsed setting were relevant to the funding being requested in the application, whilst other studies in the primary setting were not relevant.

3.4 The Subcommittee considered that the key evidence came from an open-label randomised controlled study of rituximab in both anthracycline and rituximab-naïve patients with relapsed/refractory follicular NHL (EORTC 20981, Van Oers et al Blood 2006 108:3295-3301; Van Oers et al J Clin Oncol 2010;28:2853-2858).

- 3.5 The Subcommittee noted that in this study, after a median follow-up of six years, rituximab maintenance significantly improved progression free survival (PFS) compared with observation. Members noted in the subgroup of patients who received R-CHOP induction treatment, (patients in New Zealand are likely to receive rituximab-chemotherapy as second line treatment), rituximab maintenance improved PFS by over 2 years (median, 4.4 years vs 1.9 years; $P < 0.003$; HR, 0.69). However, members noted that at five years there was no statistically significant difference in overall survival (OS) in the whole population and in the subgroup who received R-CHOP induction (HR, 0.80, $p=0.42$).
- 3.6 The Subcommittee noted that whilst no survival advantage had been demonstrated in this study, rituximab maintenance therapy was associated with a higher incidence of grade 3/4 neutropaenia (11.5% vs 6%) and more grade 3/4 infections (9.7% vs 2.4%).
- 3.7 The Subcommittee considered that the relapsed population enrolled in EORTC 20981 was rituximab and anthracycline naïve so was not representative of the current NHL population in New Zealand. Specifically most New Zealand patients would have received rituximab as part of first line treatment and many would also have received prior anthracycline treatment. Therefore, members considered that it would be inappropriate to base any funding criteria on the population enrolled in this study and similarly it would be inappropriate to extrapolate the benefits and risks seen in this study to the New Zealand population.
- 3.8 The Subcommittee noted evidence from other studies in the relapsed refractory setting. However, members considered that the evidence from these studies was weak. Members were surprised, given the individual study results, that a meta-analysis of these studies found a favourable overall survival advantage for rituximab (Vidal et al JNCI 2009;101:248-55). Members considered that the results of the meta-analysis were unreliable because the trials were heterogeneous for diagnoses, population enrolled and rituximab regimens used.
- 3.9 The Subcommittee also reviewed evidence from a randomised controlled study of rituximab maintenance compared with observation (watch and wait) following primary treatment for de novo follicular lymphoma (PRIMA, Salles et al Lancet 2011;377:42-51). Members noted that whilst rituximab maintenance significantly improved PFS compared with observation, neither overall survival nor quality of life significantly differed between the two groups. Conversely, members noted that patients treated with rituximab maintenance had significantly higher incidence of adverse events.
- 3.10 The Subcommittee considered that overall the evidence presented was disappointing and either not relevant to the relapsed/refractory NHL population in New Zealand, or the funding being sought by the supplier. Members considered that important questions regarding the longer term risks and benefits of rituximab maintenance and its place in therapy compared with the current treat-on-relapse approach remained unanswered.
- 3.11 The Subcommittee **recommended** that the application for the funding of rituximab maintenance treatment in patients with relapsed/refractory follicular NHL be declined. The Subcommittee noted that it would welcome a submission from the supplier for the use of rituximab maintenance following primary treatment including longer term data from PRIMA.

- 3.12 The Decision Criteria particularly 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*; (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.*

4 Filgrastim

- 4.1 The Subcommittee considered an application from PHARMAC staff for the listing of filgrastim in Section B of the Pharmaceutical Schedule and widening of access to non-cancer indications. The Subcommittee noted that filgrastim (Neupogen, recombinant granulocyte colony-stimulating factor 300mcg and 480mcg prefilled syringes and 300mcg vial) is currently only listed in Part II and III (Discretionary Community Supply (DCS)) of Section H of the Pharmaceutical Schedule. The Subcommittee noted that the cost of filgrastim is currently paid for from DHB hospital budgets and is currently limited on the DCS to patients with cancer. Because of these factors, the Subcommittee considered that it is possible that filgrastim is currently underutilised especially for supporting delivery of intensive chemotherapy with curative intent.
- 4.2 The Committee noted that PHARMAC had recently issued a Request for Proposals (RFP) for Hospital Supply Status and possibly Community Sole Subsidised Supply of filgrastim. The Subcommittee noted that the possibility of widening access to filgrastim was mentioned in the RFP.
- 4.3 The Subcommittee noted that the application had been reviewed by PTAC at its August 2011 meeting and noted the relevant draft PTAC minute.
- 4.4 The Subcommittee noted that multiple applications for filgrastim in neutropenia associated with non-cancer indications (autoimmune neutropenia, congenital neutropenia and infection-related neutropenia) have been received through the Exceptional Circumstances mechanism. The Subcommittee noted that filgrastim is indicated for treatment of neutropenia associated with established cytotoxic chemotherapy, peripheral blood progenitor cell mobilisation (PBPC), severe chronic neutropenia (SCN) and HIV infection.
- 4.5 The Subcommittee considered the evidence for filgrastim in non-cancer related indications and although the evidence was not as good as in cancer-related indications, the Subcommittee considered that it would be appropriate to widen access of filgrastim to these patient groups. The Subcommittee considered that treatment with filgrastim would likely reduce the risk of infection, hospitalisations and possibly mortality in these settings. There would however be an increased need for outpatient/community nursing support as some patients currently receiving filgrastim require nursing assistance for treatment administration. The Subcommittee considered that it is possible that the use of filgrastim would increase by approximately 20% from current usage if it is listed on Section B of the Pharmaceutical Schedule and access is widened to non-cancer indications.

- 4.6 [Withheld under the Official Information Act 1982, section 9(2)(b)(ii)

[redacted].

4.7 [Withheld under the Official Information Act 1982, section 9(2)(b)(i) [redacted].

4.8 The Subcommittee also commented that in the medical oncology and haematology outpatient setting, the use of pegfilgrastim had become standard practice in many centres because of the ease of use (1 dose only per cycle), better patient compliance, an increased likelihood of appropriate dosing and lower outpatient administration costs. [Withheld under the Official Information Act 1982, section 9(2)(b)(ii)]. Members considered that clinicians may still prefer to use more expensive pegfilgrastim in this setting for the reasons described above but there may be offsets to these costs in reduction of administration expenses.

4.9 The Subcommittee considered that from a clinical point of view, the importance for continuity of supply for filgrastim was very high.

4.10 The Subcommittee **recommended** that filgrastim should be listed in the Blood and Blood Forming Therapeutic Group in Section B of the Pharmaceutical Schedule subject to the following Special Authority criteria:

- Special Authority for Subsidy**
Initial application from any medical practitioner. Approvals valid without further renewal unless notified for applications meeting the following criteria:
Any of the following:
1. Prevention of neutropenia in patients undergoing high risk chemotherapy for cancer (febrile neutropenia risk $\geq 20\%^*$); or
 2. Peripheral blood stem cell mobilisation in patients undergoing haematological transplantation; or
 3. Peripheral blood stem cell mobilisation or bone marrow donation from healthy donors for transplantation; or
 4. Treatment of severe chronic neutropenia ($ANC < 0.5 \times 10^9/L$); or
 5. Treatment of drug-induced prolonged neutropenia ($ANC < 0.5 \times 10^9/L$).

Note *Febrile neutropenia risk $\geq 20\%$ after taking into account other risk factors as defined by the European Organisation for Research and Treatment of Cancer guidelines.

4.11 The Subcommittee also **recommended** that the DCS criteria be amended accordingly based on the Special Authority criteria above.

5 Review of Special Authorities

5.1 The Subcommittee reviewed a paper by PHARMAC staff regarding the removal of Special Authority restrictions from cancer pharmaceuticals.

5.2 The Subcommittee noted that currently approximately 66 cancer pharmaceuticals were funded on the Pharmaceutical Schedule, and of these, 17 are subject to Special

Authority restrictions. Members noted that PHARMAC had received requests from oncologists to remove Special Authority restrictions from a number of cancer pharmaceuticals, in particular for products that are now available as generics and have had substantial price decreases in recent years.

- 5.3 The Subcommittee noted that in reviewing the removal of Special Authority restrictions, it considered the extent of existing funding and potential new uses for each pharmaceutical, should the Special Authority restriction be removed.

Capecitabine

- 5.4 The Subcommittee considered that the current Special Authority restriction applying to capecitabine was very broad and covered most uses. Members considered that in most cases capecitabine was used as a replacement for infusional 5FU where, depending on the regimen used, the funding of capecitabine may be cost saving to DHBs.
- 5.5 The Subcommittee noted that capecitabine was associated with specific toxicities, in particular diarrhoea and dehydration, which meant it may not be an appropriate substitute in all patients currently receiving infusional 5FU treatment.
- 5.6 The Subcommittee **recommended** that the Special Authority criteria applying to capecitabine be removed. Members gave this recommendation a high priority.

Gemcitabine

- 5.7 The Subcommittee considered that the current Special Authority restriction applying to gemcitabine was very broad and covered most uses. Members considered that if the Special Authority was removed there may be increased use in earlier stage lymphoma and in late stage breast cancer.
- 5.8 The Subcommittee considered that, overall, few additional patients would be treated with gemcitabine if the Special Authority restriction was removed.
- 5.9 The Subcommittee **recommended** that the Special Authority criteria applying to gemcitabine be removed. Members gave this recommendation a high priority.

Vinorelbine

- 5.10 The Subcommittee considered that the current Special Authority restriction applying to intravenous vinorelbine was very broad and covered most uses. The Subcommittee considered that, overall, the market for vinorelbine would not grow if the Special Authority restriction was removed.
- 5.11 The Subcommittee **recommended** that the Special Authority criteria applying to intravenous vinorelbine be removed. Members gave this recommendation a high priority.

Anagrelide

- 5.12 The Subcommittee considered that the current Special Authority restriction applying to anagrelide was very broad and covered most uses. The Subcommittee considered that,

overall, the market for anagrelide would not grow if the Special Authority restriction was removed.

- 5.13 The Subcommittee **recommended** that the Special Authority criteria applying to anagrelide be removed. Members gave this recommendation a high priority

Bicalutamide

- 5.14 The Subcommittee considered that the current Special Authority restriction applying to bicalutamide covered its main use; however, members considered that there may be some increased use in locally advanced prostate cancer should the Special Authority restriction be removed.
- 5.15 The Subcommittee supported removal of the Special Authority criteria applying to bicalutamide but **recommended** that, prior to making a decision, PHARMAC staff seek further information from disease specialists regarding potential market changes.

Irinotecan

- 5.16 The Subcommittee considered that the current Special Authority restriction applying to irinotecan covered its main uses and that its toxicity would likely limit its use outside of these indications.
- 5.17 The Subcommittee supported removal of the Special Authority criteria applying to irinotecan but **recommended** that, prior to making a decision, PHARMAC staff seek further information from disease specialists regarding potential market changes.

Octreotide

- 5.18 The Subcommittee considered that the removal of the Special Authority restriction applying to octreotide (long acting formulation) would result in significant increased use. However, members considered it may be reasonable to consider removing the Special Authority restriction from the short acting preparation. Members considered that, owing to the frequency of dosing, removing the Special Authority criteria for the short acting preparation only would be unlikely to increase its use in contrast to the long acting preparation.
- 5.19 The Subcommittee supported removal of the Special Authority criteria applying to the short acting octreotide but **recommended** that, prior to making a decision, PHARMAC staff seek further information from disease specialists regarding potential market changes.

Temozolomide

- 5.20 The Subcommittee considered that the removal of the Special Authority restriction applying to temozolomide could result in significant increased use. Members considered that in particular it would likely be used in metastatic melanoma and breast cancer and that its use in brain cancer would increase.
- 5.21 The Subcommittee considered that it had insufficient information to assess the clinical need, benefits, risks and costs of temozolomide use in some of these settings and

considered that there would likely be significant financial impact from removing the Special Authority at this time.

- 5.22 The Subcommittee **recommended** that the Special Authority restriction applying to temozolomide should not be removed at this time.

Oxaliplatin

- 5.23 The Subcommittee considered that the removal of the Special Authority restriction applying to oxaliplatin would result in significant increased use. Members considered that there were a wide range of uses for oxaliplatin outside its Special Authority restriction, including pancreatic cancer, head and neck cancer and gastric/oesophageal cancers. The Subcommittee considered that if the Special Authority were removed, oxaliplatin would likely replace older, cheaper, platinum agents (cisplatin and carboplatin) and it had insufficient information to assess the clinical need, benefits, risks and costs of oxaliplatin compared with these agents, in some of these settings, at this time.
- 5.24 The Subcommittee considered that there would likely be significant financial impact from removing the Special Authority at this time.
- 5.25 The Subcommittee **recommended** that the Special Authority restriction applying to oxaliplatin should not be removed at this time.

Imatinib

- 5.26 The Subcommittee considered that the removal of the Special Authority restriction applying to imatinib mesylate would result in increased use across a range of indications. The Subcommittee considered that there would be significant financial impact from removing the Special Authority at this time. Members considered that it may be reasonable to consider removing the Special Authority restriction from imatinib in the future following generic introduction and a significant price drop.
- 5.27 The Subcommittee **recommended** that the Special Authority restriction applying to imatinib should not be removed at this time.

Others

- 5.28 The Subcommittee considered that there would be significant financial impact from removing the Special Authority restrictions applying to the remaining cancer pharmaceuticals (dasatinib, erlotinib, sunitinib, bortezomib, rituximab, thalidomide and trastuzumab). The Subcommittee **recommended** that the Special Authority restrictions applying to these pharmaceuticals should not be removed at this time.