Cancer Treatments Subcommittee of PTAC meeting held 19

November 2010

(minutes for web publishing)

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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 17 & 18 February 2011, the record of which is available on the PHARMAC website.

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1  Gemcitabine for metastatic breast cancer

1.1 The Subcommittee noted that PHARMAC had received a number of Cancer Exceptional Circumstances (CaEC) applications for the funding of gemcitabine in patients with chemotherapy sensitive metastatic breast cancer that had progressed on previous treatments. Members noted that in some cases 6th or 7th line treatment was being requested.

1.2 The Subcommittee considered that progression of metastatic breast cancer was in itself not a clinically unusual or rare situation, and therefore such funding should not, in general, be considered under the CaEC scheme unless there were some other factors which made an individuals specific situation rare or unusual.

1.3 The Subcommittee considered that it would be appropriate for PHARMAC to consider a Pharmaceutical Schedule funding application for gemcitabine for metastatic breast cancer. The Subcommittee recommended that PHARMAC staff request a funding application from the New Zealand Association of Cancer Specialists – Breast Cancer Special Interest Group.

2  Sunitinib for good prognosis advanced renal cell carcinoma

2.1 The Subcommittee considered a paper from PHARMAC staff regarding the funding of sunitinib (Sutent, Pfizer) for patients with good prognosis advanced renal cell carcinoma (RCC). Members also considered further information from the supplier and relevant correspondence received by PHARMAC in response to its recent consultation and decision to fund sunitinib for some patients with advanced RCC.

2.2 The Subcommittee noted that in August 2010 PHARMAC consulted on a proposal to fund sunitinib for patients with advanced RCC under Special Authority criteria for treatment naïve patients with intermediate or good prognosis advanced RCC. Members noted that the proposed Special Authority criteria were based on those proposed by PTAC at its November 2009 meeting.

2.3 The Subcommittee noted that in response to consultation, a group of oncologists requested that funding be limited to patients with poor and intermediate prognosis rather than intermediate and good prognosis as recommended by PTAC. Members noted that sunitinib funding for patients with poor and intermediate prognosis advanced RCC patients was implemented on 1 November 2010 and that in notifying this decision, PHARMAC invited further submissions specifically on the funding of patients with good prognosis advanced RCC for further consideration by CaTSoP and PTAC.

2.4 The Subcommittee reiterated its previous view that evidence from the pivotal phase III study (Motzer et al N Engl J Med. 2007 Jan 11;356(2):115-24 and Motzer et al J Clin Oncol 2009 August 27:3584-3590) showed that overall, in patients with advanced RCC, first line treatment with sunitinib improved progression-free survival compared with interferon alpha by approximately six months. Members noted that this evidence
comprised the primary endpoint analysis of the study which included all patients regardless of prognostic category, therefore, members considered this to be the strongest evidence from the study.

2.5 The Subcommittee noted that a secondary endpoint analysis of median overall survival demonstrated an approximate 5 month improvement in the sunitinib treated group compared with the interferon alpha treated group, however, members noted this result was not statistically significant ($p=0.051$). Members considered that this analysis was likely confounded because 25 of 375 patients treated with interferon switched to sunitinib following disease progression.

2.6 The Subcommittee reviewed evidence from a retrospective sub-analysis of the Motzer study examining the influence of baseline prognostic risk factors (favourable/good, intermediate and poor) on overall survival. Members noted that the analysis demonstrated that sunitinib increased median overall survival in intermediate and poor prognosis patients by 5 months and 1 month, respectively, compared with interferon, however, neither result was statistically significant. Members further noted that in good prognosis patients, median survival was not reached in either treatment group and at 2 years, 72% of sunitinib treated patients were alive compared with 76% of interferon treated patients.

2.7 The Subcommittee considered that the subgroup analysis by prognostic risk factor was underpowered and therefore the results should be treated with caution. Members considered that it was not possible to conclude with certainty at this time whether or not good prognosis patients would benefit from sunitinib treatment compared with interferon.

2.8 The Subcommittee considered that ideally sunitinib should be funded for all patients with advanced RCC, however, given its high cost, members considered that limiting funding to intermediate and poor prognosis patients was a pragmatic decision made by PHARMAC.

2.9 The Subcommittee considered that good prognosis patients with progressive disease may benefit from sunitinib treatment, and noted that in most cases such patients would likely have symptoms that would characterise them as intermediate prognosis in which case they would be eligible for funding.

2.10 The Subcommittee reiterated its view that sunitinib is, essentially, a very high-cost palliative treatment and recommended that the funding of sunitinib for patients with good prognosis advanced RCC be declined.

2.11 The Decision Criteria particularly relevant to this recommendation are: (i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Māori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government’s overall health budget) of any changes to the Pharmaceutical Schedule.

2.12 The Subcommittee considered that for clarity the current Special Authority criteria should be amended to include the actual prognostic risk factors used to define poor and
intermediate risk groups, therefore, members recommended that the criteria be amended as follows (changes in bold and strikethrough):

Initial application only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months for applications meeting the following criteria:
All of the following:
1. The patient has metastatic renal cell carcinoma; and
2. Either
   2.1 The patient is sunitinib treatment naïve; or
   2.2 The patient received sunitinib prior to 1 November 2010 and disease has not progressed; and
3. The patient has good performance status (WHO/ECOG grade 0-1); and
4. The disease is of predominant clear cell histology; and
5. The patient has intermediate or poor prognosis based on the NCCN clinical practice guidelines for kidney cancer defined as:
   At least one of the following:
   5.1 Lactate dehydrogenase level > 1.5 times upper limit of normal; or
   5.2 Haemoglobin level < lower limit of normal; or
   5.3 Corrected serum calcium level > 10 mg/dL (2.5 mmol/L); or
   5.4 Interval of < 1 year from original diagnosis to the start of systemic therapy; or
   5.5 Karnofsky performance score of ≤ 70; or
   5.6 ≥ 2 sites of organ metastasis; and
6. Sunitinib to be used for a maximum of 2 cycles.

Renewal only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months for applications meeting the following criteria:
Both:
1. No evidence of disease progression; and
2. The treatment remains appropriate and the patient is benefiting from treatment.

Notes:
Sunitinib treatment should be stopped if disease progresses.

3 Nab-paclitaxel (Abraxane) for advanced breast cancer

3.1 The Subcommittee considered an application from Specialised Therapeutics Limited for the funding of nab-paclitaxel (Abraxane) for the treatment of patients with metastatic breast cancer after failure of prior therapy including an anthracycline.

3.2 The Subcommittee noted that two taxanes, paclitaxel and docetaxel, were currently fully funded for the treatment of patients with metastatic breast cancer. Members considered that paclitaxel and docetaxel had similar activity in patients with metastatic breast cancer, however, there were dose, schedule and toxicity differences between the two taxanes.
3.3 The Subcommittee considered that in New Zealand paclitaxel administered weekly (80mg/m² IV over one hour) was a commonly used first line taxane treatment in patients with metastatic breast cancer, with docetaxel administered every 3 weeks (75 mg/m² IV) the most common second line treatment. However, members noted that some oncologists preferred to use docetaxel first, followed by paclitaxel and that treatment choice was also influenced by whether or not the patient had received prior adjuvant taxane therapy.

3.4 The Subcommittee considered that nab-paclitaxel was a novel formulation of the taxane paclitaxel which removed the need for corticosteroid and antihistamine premedication required with the standard paclitaxel formulation.

3.5 The Subcommittee considered evidence from three randomised controlled studies in patients with metastatic breast cancer, two comparing nab-paclitaxel with paclitaxel (CA012 and CA201) and the third comparing nab-paclitaxel with docetaxel (CA024).

3.6 The Subcommittee considered that the evidence demonstrated that nab-paclitaxel was at least as effective as docetaxel 100 mg/m² administered every three weeks or paclitaxel 175 mg/m² administered every three weeks. However, members noted that there was no evidence comparing nab-paclitaxel with weekly paclitaxel, and members considered that weekly paclitaxel was more efficacious than 3 weekly paclitaxel. Members also noted that the dose of docetaxel administered in CA024 was higher (100 mg/m²) than that most commonly used in practice (75-80 mg/m²), which would result in higher rates of toxicity, most importantly febrile neutropaenia.

3.7 The Subcommittee considered that the supplier’s estimate of the number of patients that would be treated with nab-paclitaxel was too low. Members considered that if funded, nab-paclitaxel would replace paclitaxel, either as first or second line treatment depending on the treating oncologists’ current taxane sequence preferences.

3.8 The Subcommittee considered that the main benefit of nab-paclitaxel compared with paclitaxel was its lack of allergenic risk. Members considered that although the annual incidence of hypersensitivity reactions to paclitaxel was low, significant resource was required to minimise the risk of hypersensitivity reactions in patients treated with paclitaxel, namely, pre-medication and patient and nurse education on symptoms and treatment. Members also noted that because it is administered only once every three weeks, treatment with nab-paclitaxel would require less nursing resource and infusion time compared with weekly paclitaxel.

3.9 The Subcommittee **recommended** that nab-paclitaxel should be funded on the Pharmaceutical Schedule for the treatment of patients with metastatic breast cancer after failure of prior therapy including an anthracycline only if cost neutral to weekly paclitaxel and 3 weekly docetaxel. Members considered that cost estimates should include drug pharmaceutical and other health sector costs and cost offsets including administration, toxicity treatment and hypersensitivity prevention, education and resources.

3.10 The Decision Criteria particularly relevant to this recommendation are: (i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Māori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding
pharmaceuticals rather than using other publicly funded health and disability support services

4 Lapatinib for Her 2 positive advanced breast cancer

4.1 The Subcommittee considered an application from the New Zealand Association of Cancer Specialists – Breast Special Interest Group (BSIG) for the funding of lapatinib (Tykerb) for patients with trastuzumab-resistant metastatic HER-2 positive breast cancer, either as single agent therapy or in combination with chemotherapy as selected by the patient’s Medical Oncologist.

4.2 The Subcommittee noted that in November 2007 PTAC had considered a funding application for the same population from the supplier of lapatinib, GlaxoSmithKline. Members noted that at that time PTAC recommended the application be declined and CaTSoP, having reviewed PTAC’s minute at its March 2008 meeting, agreed.

4.3 The Subcommittee reviewed evidence provided by BSIG which included studies examining the use of lapatinib both in the first line treatment of metastatic disease, and in patients who have progressed following previous trastuzumab treatment for their metastatic disease.

4.4 The Subcommittee considered that there was no new evidence provided in the application that was directly relevant to the funding request (i.e. in trastuzumab-resistant patients in combination with chemotherapy), compared with that reviewed by PTAC in 2007. Members considered that the only evidence directly relevant to the applicant’s request for funding was from a Phase III study comparing lapatinib plus capecitabine or capecitabine alone in patients with HER2-positive, locally advanced or metastatic breast cancer that has progressed after treatment with an anthracycline, a taxane, and trastuzumab (study EGF100151 Geyer et al New Eng J Med 2006), which, had previously been reviewed by PTAC.

4.5 The Subcommittee considered that evidence from the EGF100151 study demonstrated that the addition of lapatinib to capecitabine improved response rate and time to disease progression, however, the magnitude of benefit was small and there was no clear evidence of any survival benefit.

4.6 The Subcommittee considered that other evidence provided (mainly single arm Phase I and II studies of lapatinib in the first line and trastuzumab resistant metastatic breast cancer settings and one phase III study (EGF30008) of lapatinib with letrozole in first-line metastatic breast cancer patients, including a population with known HER2 positive disease (Johnston et al J Clin Oncol 2009)), although not directly relevant to the application did demonstrate that lapatinib had activity in patients with HER2 positive metastatic disease.

4.7 The Subcommittee considered that although there were no head to head studies directly comparing lapatinib with trastuzumab (Herceptin, Roche), it was likely that the two treatments would be similar. Members noted that, being an oral treatment, lapatinib would be significantly easier to administer compared with trastuzumab, which would be an advantage. Members also considered that, theoretically, because of its mode of
action, in particular crossing the blood brain barrier, lapatinib may be more efficacious in some settings than trastuzumab.

4.8 The Subcommittee **recommended** that lapatinib should be funded for patients with HER2-positive, locally advanced or metastatic breast cancer that has progressed after treatment with an anthracycline, a taxane, and trastuzumab. However, members considered that lapatinib was an expensive treatment and the evidence was limited and had not significantly progressed since 2007 and therefore gave this recommendation a low priority.

4.9 The Decision Criteria particularly relevant to this recommendation are: (i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Māori and Pacific peoples; (iii) The availability and suitability of existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government’s overall health budget) of any changes to the Pharmaceutical Schedule.

4.10 The Subcommittee noted that it wished to consider a funding application for lapatinib as first line treatment in HER2-positive patients with metastatic breast cancer in place of currently funded trastuzumab.

5 Trastuzumab retreatment and treatment beyond progression

5.1 The Subcommittee considered an application from the New Zealand Association of Cancer Specialists – Breast Special Interest Group (BSIG) for retreatment with trastuzumab after adjuvant therapy, and treatment beyond progression in metastatic disease, in patients with HER 2 positive metastatic breast cancer.

5.2 The Subcommittee noted that the application was prompted by its review of the Special Authority criteria for trastuzumab at its April 2010 meeting.

_Treatment beyond disease progression_

5.3 The Subcommittee considered that the evidence to support continued treatment with trastuzumab beyond disease progression in patients with HER 2 positive metastatic breast cancer was of poor quality and limited with no completed phase 3 evidence. Members also noted a recent publication concluded that the use of continued trastuzumab beyond disease progression was poorly cost-effective (Matter-Walstra et al Annals of Oncology 21: 2131–2134, 2010).

5.4 The Subcommittee considered that despite the lack of reliable evidence some oncologists may be continuing to use trastuzumab beyond disease progression in patients with HER 2 positive metastatic breast cancer. Members considered that in such cases the background chemotherapy regimen would be changed on disease progression but trastuzumab treatment would be continued.
5.5 The Subcommittee noted that because the initial approval period for trastuzumab in the metastatic setting was 12 months some oncologists may be using it for the full 12 months despite disease progression. Members also considered that funding for these patients under the current Special Authority Renewal criteria “the cancer has not progressed” was somewhat ambiguous. Members considered that some oncologists appear to have considered that this means the cancer was not progressing at the time of applying for the renewal (rather than at any time during the previous 12 month approval period). Members considered this inappropriate and considered that trastuzumab should be discontinued if there is evidence of tumour progression at any time.

5.6 The Subcommittee considered that continuing treatment with trastuzumab beyond disease progression in patients with HER 2 positive metastatic breast cancer was not appropriate.

5.7 The Subcommittee **recommended** that the application for funding of further trastuzumab treatment for HER 2 positive metastatic breast cancer following disease progression on trastuzumab, should be declined because it was inappropriate (and not cost-effective). Members considered that treatment with trastuzumab should be discontinued at the time of tumour progression and further applications should be declined.

5.8 The Subcommittee **recommended** that the Special Authority criteria for trastuzumab be amended to clarify funding as follows (changes in bold and strikethrough):

**Initial application — (metastatic breast cancer)** only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months where the patient has metastatic breast cancer expressing HER-2 IHC 3+ or FISH+ and disease does not progress while on treatment.

**Renewal — (metastatic breast cancer)** only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:
- Both:
  - 1 The patient has metastatic breast cancer; and
  - 2 The cancer has not progressed at any timepoint during the previous 12 months.

**Initial application — (early breast cancer)** only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 15 months for applications meeting the following criteria:
- All of the following:
  - 1 The patient has early breast cancer expressing HER 2 IHC 3+ or ISH + (including FISH or other current technology); and
  - 2 Maximum cumulative dose of 106 mg/kg (12 months’ treatment); and
  - 3 Any of the following:
    - 3.1 9 weeks’ concurrent treatment with adjuvant chemotherapy is planned; or
    - 3.2 12 months’ concurrent treatment with adjuvant chemotherapy is planned; or
    - 3.3 12 months’ sequential treatment following adjuvant chemotherapy is planned; or
    - 3.4 Other treatment regimen, in association with adjuvant chemotherapy, is planned.

**Note:** For patients with previous Special Authority approvals for a maximum cumulative dose of 20 mg/kg (9 weeks treatment) granted after 1 April 2009 the approval period has been extended to allow claims for a maximum cumulative dose of 106 mg/kg (12 months treatment).
Re-treatment

5.9 The Subcommittee considered that there was limited evidence to support trastuzumab retreatment when given for metastatic breast cancer after disease progression following prior adjuvant trastuzumab treatment for early breast cancer. Members noted that in the early breast cancer setting trastuzumab was administered for a predefined time period (either 9 weeks or 12 months) whereas in the metastatic setting treatment was administered until disease progression.

5.10 The Subcommittee considered that there was some evidence to suggest that if a patient’s disease remained controlled for a prolonged period after treatment with trastuzumab in the early breast cancer setting it was likely that it would respond on re-use, following disease progression to metastatic breast cancer.

5.11 The Subcommittee considered that in the case of a patient progressing during the first few months of treatment with trastuzumab for early breast cancer it was likely that they actually presented with undetectable metastases at baseline and should have been treated as having had metastatic disease from the beginning, rather than having treatment stopped after a defined time period. Members considered that technically this would also be considered retreatment.

5.12 The Subcommittee considered that in the case of a patient progressing within the first few months after stopping treatment with trastuzumab for early breast cancer, it was likely that they actually had had undetectable metastases at baseline and should have been treated as having had metastatic disease from the start, rather than having treatment stopped after a pre-defined time period (9 weeks or 12 months). Members considered that technically this would also be considered retreatment.

5.13 The Subcommittee recommended that trastuzumab should be funded for patients with HER 2 positive metastatic breast cancer after disease progression following prior adjuvant trastuzumab treatment for early breast cancer. Members gave this recommendation a high priority. The Subcommittee considered that the current Special Authority criteria already covered trastuzumab retreatment and therefore its recommendation would have no financial impact.

6 Bortezomib for t(4;14) multiple myeloma

6.1 The Subcommittee considered an application from a clinician for the funding of bortezomib (Velcade) for the treatment of patients with newly diagnosed multiple myeloma with high risk t(4;14) cytogenetic abnormality. Members noted that the application had been prompted by a review of Cancer Exceptional Circumstances (CaEC) applications it conducted at its November 2009 meeting.

6.2 The Subcommittee noted that it had previously considered the funding of bortezomib for patients with multiple myeloma in different settings on a number of occasions, however, it had not previously considered its funding in the first line setting prior to stem cell transplantation.
6.3 The Subcommittee considered that whilst the disease was not curable, prognoses for patients with multiple myeloma were hugely variable with age, stage and genotype all influencing disease prognoses.

6.4 The Subcommittee considered that specific genotypes of multiple myeloma, principally those with deletions in chromosomes 13 or 13q and 17p or translocation t(4;14), were associated with poorer outcome and often more than one abnormality was present in the abnormal clones.

6.5 The Subcommittee considered that approximately 10% of patients with multiple myeloma would carry the t(4;14) genotype. Members noted that usually their disease would initially respond well to treatment however they would relapse quicker than wild type multiple myeloma and therefore had poorer long term outcomes. Members considered that the average survival in these patients was only around 1.5-2 years with conventional treatments.

6.6 The Subcommittee considered that the evidence for bortezomib in newly diagnosed t(4;14) multiple myeloma was weak with the main evidence being from a retrospective analysis of a case series of 507 patients with newly diagnosed MM who received four cycles of bortezomib-dexamethasone induction therapy before high-dose melphalan (Vel/Dex) either in the French IFM 2005-01 study or subsequently treated according to this study protocol after study closure (Avet-Loiseau et al J Clin Oncol 2010 Oct 20;28(30):4630-4). Members noted that this population was compared with a control group comprising a case series of 521 patients with newly diagnosed MM treated with four cycles of vincristine, doxorubicin and dexamethasone induction therapy (VAD) with outcomes analyzed by presence or absence of t(4;14) and/or del(17p) cytogenetic abnormalities. Members noted that approximately one third of patients went on to receive lenalidomide maintenance therapy in study IFM 2005-02.

6.7 The Subcommittee noted that overall the presence of t(4;14) and/or del(17p) was associated with a worse outcome in both treatment groups (Vel/Dex or VAD) compared with patients who had wild-type disease. However, when compared with VAD induction, Vel/Dex induction did appear to improve outcomes (Event Free Survival and Overall Survival) in patients with t(4;14) but not those with del(17p).

6.8 The Subcommittee considered that whilst the evidence was weak it did appear that induction treatment with bortezomib could, to some extent improve outcomes in patients with t(4;14) multiple myeloma such that prognosis was similar to other patients with multiple myeloma without t(4;14) treated with current standard (non-bortezomib) treatments. Members considered that if funded as de novo (first line) treatment for patients with t(4;14) myeloma who were transplant eligible, approximately 10 patients per annum would be eligible for bortezomib treatment.

6.9 The Subcommittee recommended that bortezomib should be funded for patients with newly diagnosed t(4;14) multiple myeloma who are planned to receive a stem cell transplant. Members considered that in this setting, bortezomib induction should be administered as per the IFM 2005-01 study. The Subcommittee gave this recommendation a high priority.

6.10 The Decision Criteria particularly relevant to this recommendation are: (i) The health needs of all eligible people within New Zealand; (ii) 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.

7 Bortezomib for AL amyloidosis

7.1 The Subcommittee considered an application from a clinician for the funding of bortezomib (Velcade) for the treatment of patients with systemic AL amyloidosis. Members noted that the application had been prompted by a review of Cancer Exceptional Circumstances (CaEC) applications it conducted at its November 2009 meeting. The Subcommittee noted that 18 CaEC applications for bortezomib for patients with AL amyloidosis had been received by PHARMAC since July 2009.

7.2 The Subcommittee considered that AL amyloidosis was a rare disease in which the rapid accumulation of amyloid protein caused death from organ failure, most commonly sudden cardiac failure. Members noted that AL amyloidosis is frequently diagnosed late and because of multiple organ involvement these patients were often very ill and consequently difficult to treat.

7.3 The Subcommittee considered that the application was of very high quality being clear, balanced and concise. However, members considered that the current evidence available to support use of bortezomib in AL Amyloidosis patients was weak, comprising only single arm case series studies and conceptual (mode of action) arguments.

7.4 The Subcommittee considered that whilst there were good disease biology and mode of action arguments in favour of extrapolating the results of bortezomib studies from the multiple myeloma setting to the AL amyloidosis setting, significant differences between the two diseases meant that this approach was not without its limitations. For example, the organ involvement in AL amyloidosis patients would likely result in higher rates of bortezomib-associated adverse events which may significantly change the risk benefit profile of bortezomib in this population. Therefore, members considered that it was important for good evidence to be generated specifically for patients with AL amyloidosis and noted that a Phase III study to address this was underway.

7.5 The Subcommittee considered that bortezomib’s ability to produce rapid complete haematological responses, as demonstrated in patients with multiple myeloma, may be of particular importance for patients with AL Amyloidosis, especially those with cardiac involvement whom members considered to be at greatest risk of sudden death.

7.6 The Subcommittee considered that currently in New Zealand most patients with AL amyloidosis would be treated with melphalan and dexamethasone, or cyclophosphamide, thalidomide and dexamethasone with occasional highly selected patients progressing to an autologous stem cell transplantation. Members noted that although thalidomide is not specifically funded for AL Amyloidosis the similarity between this disease and multiple myeloma meant that some patients would be described as ‘myeloma’ for the purposes of funding. Members considered that if funded bortezomib
would be given in addition to currently funded treatments, with regimens based on those used for patients with multiple myeloma. Members considered that it was reasonable to apply a stopping rule such that if patients had not responded after 2 cycles of treatment it would be stopped.

7.7 The Subcommittee considered around 20 of patients per year would be treated with bortezomib for AL amyloidosis if it were funded.

7.8 The Subcommittee **recommended** that bortezomib should be funded on the Pharmaceutical Schedule for the treatment of patients with systemic AL Amyloidosis under Special Authority criteria as follows:

**Initial application** only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months for applications meeting the following criteria:

All of the following:
1. The patient has newly diagnosed systemic AL Amyloidosis; and
2. Bortezomib to be administered in combination with chemotherapy and steroids; and

**Renewal** only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:

Both:
1. The patient’s disease has responded (minimum 25% reduction in serum-free light chain concentration) to treatment with bortezomib at the completion of cycle 2; and
2. Maximum of 4 further treatment cycles.

7.9 The Subcommittee noted that its recommendation was based on weak clinical evidence but took into account the high unmet medical need in this population and conceptual arguments, therefore members gave the recommendation a medium priority. Members considered that the priority would improve if evidence from the ongoing Phase III study was supportive and recommended that the applicant resubmit once this data becomes available.

7.10 The Decision Criteria particularly 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**.

**8 Bortezomib for multiple myeloma as bridge to transplant**

8.1 The Subcommittee reviewed a paper prepared by PHARMAC staff regarding applications for the funding of bortezomib (Velcade) as a bridge to transplant which has been considered under the Cancer Exceptional Circumstances (CaEC) scheme.

8.2 The Subcommittee noted that since May 2010 PHARMAC has received 5 CaEC applications for bortezomib in patients with multiple myeloma for use as a bridge to stem cell transplantation after failure of, or intolerance to, at least one prior treatment. Members noted that some of these patients also had renal impairment and applicants considered that bortezomib was particularly useful in this population.
8.3 The Subcommittee considered that evidence from a sub study of the VISTA trial, which compared bortezomib in combination with melphalan and prednisone (BMP) with MP alone in patients with previously untreated MM ineligible for high dose chemotherapy or transplant, demonstrated that bortezomib benefit was maintained in patients with impaired renal function (Dimopoulos et al J Clin Oncol. 2009 Dec 20;27(36):6086-93).

8.4 The Subcommittee considered that, at least in younger patients, high dose chemotherapy followed by stem cell transplant was the current standard first line treatment for multiple myeloma throughout the world. However, members considered that the strength and quality of the evidence to support this treatment choice was variable and is based on comparison of high dose chemotherapy and stem cell transplant strategies with conventional treatment with alkylating agents and steroids without stem cell transplant. Members noted that although at least three randomised studies had demonstrated progression free and overall survival benefit for autologous transplant when high dose melphalan is used as the conditioning regimen, a recent meta analysis did not find any survival benefit for transplant.

8.5 The Subcommittee considered that the potential benefits of transplantation needed to be carefully balanced with the known risks, including transplant related mortality which is about 1-2%. Members noted that even where stem cell transplantation was performed it was not curative and treatment goals were at best to improve quality of life and delay onset and severity of symptoms.

8.6 The Subcommittee considered that although bortezomib appeared to be a reasonable option for patients who fail to respond, or are unable to tolerate, standard high dose chemotherapy treatment prior to stem cell transplant, there was no evidence that it was any better than other treatment options in this setting. Members considered that high dose dexamethasone was a reasonable treatment choice for patients with renal impairment. Members further considered that the majority of patients with renal impairment can be treated, and would benefit from, standard treatment options.

8.7 The Subcommittee deferred making a recommendation on the funding of bortezomib as a bridge to transplant pending further comparative evidence becoming available.

9 Deferasirox and deferiprone for chronic iron overload

9.1 The Subcommittee reviewed applications from Novartis for deferasirox (Exjade) and Orphan Australia for deferiprone (Ferriprox) for the treatment of chronic transfusional iron overload secondary to congenital and acquired anaemias. The Subcommittee noted that deferiprone is currently funded for the treatment of transfusional iron overload secondary to congenital anaemias. The Subcommittee also noted that these applications included information reviewed by PTAC at its August 2010 meeting and also new information available since then, provided by the suppliers.

9.2 The Subcommittee considered that both deferiprone and deferasirox had similar clinical efficacy and both had a place in iron chelation therapy. The Subcommittee considered that deferiprone was more effective than deferasirox in removing cardiac iron and can be used as monotherapy or in combination with desferrioxamine in patients with significant cardiac iron overload.
9.3 The Subcommittee considered that the risk of agranulocytosis with deferiprone was reversible and manageable with regular blood monitoring. The Subcommittee considered that weekly blood monitoring was appropriate during the first year of therapy but could possibly be extended to monthly blood monitoring after that. The Subcommittee also noted that in clinical trials, deferiprone was associated with other side-effects; thrombocytopenia in the absence of splenomegaly in up to 46% of patients, gastrointestinal side-effects like diarrhoea and vomiting in 4 to 46% of patients and arthropathy in up to 20% of patients. In some patients, the arthropathy was not reversible.

9.4 The Subcommittee considered that deferasirox had compliance benefits with being a once daily treatment and there is currently more evidence for its use in children < 6 years of age than deferiprone. However, the Subcommittee considered that desferrioxamine should still be first-line treatment in children <6 years of age. The Subcommittee considered that deferasirox has been shown to effectively reduce the level of labile plasma iron levels which is a surrogate marker of iron load but its significance in the long term is still currently unknown. Members also considered that deferasirox was associated with renal impairment and failure in some patients which is a significant issue considering patients could be on lifelong therapy. The Subcommittee also noted that currently deferasirox is significantly more expensive than deferiprone. The Subcommittee considered that once a patient is commenced on one oral iron chelator; either deferiprone or deferasirox, clinicians would be unlikely to switch patients to the other treatment unless medically necessary as this would expose the patient to the potential side-effects of both drugs.

9.5 The Subcommittee considered that treatment with oral iron chelation therapy was appropriate in some patients with transfusional iron overload in some acquired anaemias such as acquired red cell aplasia as some of these patients are at risk of significant iron overload not unlike patients with congenital inherited anaemias. The Subcommittee considered that there are only 5 to 6 patients in New Zealand with these conditions as they are very rare. However, the Subcommittee considered that venesection rather than iron chelation therapy was more appropriate treatment for patients with transfusional iron overload post-stem cell transplant and that patients with paroxysmal nocturnal haemoglobinuria do not develop iron overload significant enough to require iron chelation.

9.6 The Subcommittee noted the evidence for deferasirox and deferiprone in myelodysplasia was mainly non-randomised, retrospective and small prospective studies. There was more clinical evidence currently available for deferasirox rather than deferiprone. These studies showed that deferasirox or iron chelation therapy was able to reduce body iron (including Gattermann et al 2008; Blood (ASH Annual Meeting Abstracts) 2008 112: Abstract 633). Some of these studies also showed that iron chelation therapy is able to increase the overall survival of patients with MDS, especially the ones with low or int-1 risk (including Fox et al 2009. ASH Abstract 1747 and Raptis et al; Transfusion. 2010 Jan;50(1):190-9). The Subcommittee considered that the entry criteria for iron chelation were different in the different studies and there was a risk of significant bias in selecting patients as age and transfusion status could all affect the results. The Subcommittee noted that the risk of progression to acute myeloid leukaemia (AML) was similar in patients with MDS whether they received iron chelation or not (Fox et al 2009. ASH Annual Meeting Abstracts 2009; Abstract 1747). The Subcommittee also noted that the study by Rose et al (Leuk Res. 2010 Jul; 34(7): 864-70) had shown a decreased rate of
death from AML in the group which received iron chelation therapy but that this was not statistically significant and considered that although a number of clinical guidelines suggest the use of iron chelating agents in patients with MDS and iron overload, evidence from randomised studies is needed to show that iron chelation reverses iron-related organ damage, reduces morbidity and prolongs survival. Members noted that a multi-centre, randomised, double blind, placebo controlled study sponsored by Novartis (TELESTO trial) designed to address this question has recently started recruiting patients.

9.7 The Subcommittee also noted that there were a series of case reports recently published showing that some patients with acquired anaemias receiving deferasirox showed a decrease in transfusion requirements. The Subcommittee noted that the mechanisms for such phenomenon were still unclear but that NF-kB downregulation could be involved.

9.8 The Subcommittee **recommended** that deferasirox is funded with medium priority for patients with transfusional iron overload secondary to congenital anaemias and restricted via the following Special Authority due to its high cost:

Special Authority for Subsidy

Initial application only from a relevant specialist. Approvals valid without further renewal unless notified for applications meeting the following criteria:

All of the following:

1. The patient has been diagnosed with chronic transfusional iron overload due to congenital inherited anaemia; and
2. Either
   1. The patient is <6 years of age; or
   2. Treatment with maximum tolerated doses of deferiprone have proven ineffective as measured by serum ferritin levels, MRI T2* or liver biopsy; or
   3. Treatment with deferiprone has resulted in intolerable gastrointestinal side-effects like nausea, vomiting or diarrhoea; or
   4. Treatment with deferiprone has resulted in arthralgia or arthritis; or
   5. Treatment with deferiprone has resulted in agranulocytosis.

9.9 The Subcommittee **recommended** that an oral iron chelator, either deferiprone or deferasirox (or both), be funded with medium priority for patients with transfusional iron overload due acquired red cell aplasia.

9.10 The Subcommittee **recommended** that the funding of an oral iron chelator for transfusional iron overload secondary to stem cell transplants and myelodysplasia be declined.

9.11 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; (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government’s overall health budget) of any changes to the Pharmaceutical Schedule.