Cancer Treatments Subcommittee of PTAC (CaTSoP) meeting held

20 November 2009

(minutes for web publishing)

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Note that this document is not necessarily a complete record of the CaTSoP meeting; under the Terms of Reference, only the relevant portions of minutes relating to CaTSoP discussions about applications or PHARMAC staff proposals that contain a recommendation are generally published.

CaTSoP 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.

Some material has been withheld, in accordance with the Official Information Act 1982 (OIA), in order to protect the privacy of natural persons (section 9(2)(a)).

These Subcommittee minutes were reviewed by PTAC at its meeting on 25 & 26 February 2010, the record of which is available on the PHARMAC website.

Contents

1. Deferasirox and deferiprone for chronic iron overload

1.1. The Subcommittee requested an update on the funding of oral iron chelating agents. PHARMAC staff indicated that they were in negotiation with suppliers but it was unlikely that anything would be funded in this financial year due to lack of available funding.

1.2. Members noted that at its 25 June 2009 meeting the Subcommittee had agreed with PTAC's view that an oral agent should be funded for patients with chronic transfusional iron overload due to congenital inherited anaemias. The Subcommittee considered that this was the group of patients with the highest unmet clinical need, and **recommended** that an oral agent be funded for these patients with a high priority.

1.3. Members considered that funding for the other patient groups identified was lower priority, such that consideration of funding for these patients should not delay, or prevent, funding for patients with congenital inherited anaemias. In particular, members considered that there was a significant risk of 'slippage' associated with funding of patients with low risk myelodysplastic syndromes (MDS). Members considered that a proportion of MDS patients could potentially benefit from iron chelating agents given parenterally or orally, in particular those with a prognosis from myelodysplasia of several years without competing risks of mortality. Members noted that according to Malcovati et al JCO 2007; 25: 3503 patients with very low, or low, risk MDS have median survival in excess of 5 years and comprise 30-50% of all MDS patients. Members considered that such patients when treated with iron chelation have a reduced risk of cardiac death secondary to iron overload, however, other causes of death are not obviously reduced, and members noted that many patients with low risk MDS die from non-cardiac causes. Members considered that although iron chelation treatment is appropriate for many low risk MDS patients, and despite desferioxamine being funded, currently very few patients are treated because of the inconvenience of its administration. Members considered that if an oral iron chelating agent was funded for patients with low risk MDS there was a considerable risk that uptake could be very high due to the convenience of oral treatment compared with multiple injections. Members considered that if oral iron chelating agents were funded for patients with MDS and other acquired iron overload disorders it would be necessary to carefully define funding criteria to avoid the risk of significant 'slippage'.

2. Bortezomib CUA

2.1. The Subcommittee noted correspondence between PHARMAC staff and some members of the Subcommittee regarding the PHARMAC cost-utility analysis (CUA) for bortezomib in relapsed/refractory multiple myeloma. The Subcommittee noted that the PHARMAC CUA and associated Technology Assessment Report (TAR) were reviewed by PTAC at its August 2009 Meeting. Members noted that the full minute was provided. Members noted that the minute had been provided to the supplier and some haematologists and there had been some discussion of the CUA model at a recent Ministry of Health Haematology working group meeting.

2.2. The Subcommittee noted that the CUA compared bortezomib plus dexamethasone with thalidomide plus dexamethasone. Members noted that since there have been

no clinical trails directly comparing bortezomib with thalidomide, the CUA necessarily included a number of assumptions regarding the relatively efficacy of the two treatments.

2.3. The Subcommittee noted that the efficacy gains for bortezomib in the CUA model were based on the progression-free survival and overall survival gains for bortezomib compared with dexamethasone alone in the APEX study. Members considered that using the APEX efficacy gains in the model, would likely overestimate the benefit of bortezomib plus dexamethasone over thalidomide plus dexamethasone since thalidomide could be regarded as a more effective agent than dexamethasone in relapsed multiple myeloma. However, the actual gains were unknown since there were no comparative studies.

2.4. The Subcommittee noted that rather than reduce the efficacy gains in the CUA model PHARMAC staff had instead used a shorter duration of treatment for the comparator arm (thalidomide plus dexamethasone) than would be expected in clinical practice. Members noted that this approach reduced the costs of the comparator arm which essentially acted as a proxy for reducing the efficacy gains of bortezomib over the comparator.

2.5. The Subcommittee considered that the PHARMAC CUA model was legitimate but **recommended** that, ideally, the comparator arm the model should reflect current clinical practice, which members considered would be on average 10 months of thalidomide treatment. Members **recommended** that, in the event that the comparator arm was modelled as such, the efficacy gains for bortezomib in the CUA model should be reduced from those currently used in the model, which are based on the APEX study. Members noted that the outcome of PHARMAC CUA did not change significantly when the model was adjusted accordingly.

2.6. The Subcommittee considered that the inputs for the comparator arm in the PHARMAC CUA models for both bortezomib and lenalidomide in relapsed/refractory multiple myeloma should be consistent.

2.7. The Subcommittee considered that the patient number estimates in the supplier's submission, 27 in the first year rising to 108 by year 3, were too low. Members considered that given that multiple myeloma is incurable, most patients would require second-line treatment; therefore, it would be expected that uptake would be rapid such that by year 4, up to 250 patients would access second line treatment and after that the number of patients per year would remain fairly stable at around 250 per year with growth equal to that of new multiple myeloma diagnoses. Members consider that, if funded, bortezomib would likely replace thalidomide as the preferred second-line treatment.

3. Review of Cancer Exceptional Circumstances (Cancer EC) Applications

3.1. The Subcommittee reviewed a paper prepared by PHARMAC staff regarding applications for funding of cancer treatments which had been considered under the Cancer EC scheme.

3.2. The Subcommittee did not identify any treatments that it could recommend at this stage either for a Pharmaceutical Schedule listing or any treatments that should not continue be funded through the Cancer EC scheme, at least in the short term.

3.3. The Subcommittee noted that amsacrine and thiotepa had been listed under Section 29 of the Medicines Act 1981 on the Pharmaceutical Schedule from 1 August 2009.

3.4. The Subcommittee noted that there are certain DHBs which do not fund any treatments under the Cancer EC scheme; therefore, there is currently an inequity in access to some treatments between DHBs.

3.5. As requested by PHARMAC staff, the Subcommittee specifically reviewed the following treatments that PHARMAC staff identified as being the subject of a number of Cancer EC applications (each is discussed separately, below):

1. Bortezomib for amyloidosis;
2. Bortezomib for IgA/IgG/t(4:14 translocation) Multiple Myeloma / Plasma Cell Leukaemia;
3. Azacitadine for transfusion dependent Acute Myeloid Leukaemia / Myelodysplastic Syndrome;
4. Pipobroman for polycythemia / essential thrombocythaemia;
5. Rabbit anti-thymocyte globulin for GvHD prophylaxis.

3.6. Bortezomib for amyloidosis

3.6.1. The Subcommittee noted that bortezomib is currently being funded under the Cancer EC scheme for a small population of patients with amyloidosis. The Subcommittee reviewed the supporting literature supplied with the relevant Cancer EC applications.

3.6.2. The Subcommittee considered that amyloidosis was a clonal disorder, or a plasma cell dyscrasia which is a sub-group of myeloma. The Subcommittee considered that it was appropriate to classify amyloidosis as a cancer. Members considered the patients could be grouped and defined as patients with primary AL (amyloid light chain) amyloidosis.

3.6.3. The Subcommittee noted that the current Cancer EC scheme enabled the funding of bortezomib in amyloidosis patients ahead of funding this treatment for multiple myeloma patients, the subject of funding applications from the supplier.

3.6.4. The Subcommittee considered that thalidomide, bortezomib or lenalidomide have been used as treatments for patients with amyloidosis since they were introduced for the treatment of patients with myeloma. Members considered that a minority of patients with amyloidosis may undergo high dose chemotherapy and stem cell transplant as part of their treatment, but most patients, particularly those with cardiac involvement, were too unwell for this approach. Members considered that low dose melphalan and prednisone or melphalan plus dexamethasone were used if thalidomide, bortezomib or lenalidomide were not available.

3.6.5. The Subcommittee considered that efficacy data and case series for the use of bortezomib in amyloidosis were limited; however, members acknowledged that they were aware of local anecdotal reports of very successful outcomes in

amyloid patients treated with bortezomib. The Subcommittee advised that there is an international randomised controlled study comparing melphalan plus dexamethasone with melphalan, dexamethasone and bortezomib (BMDex) for untreated patients ineligible for stem cell transplant with stage I or II amyloidosis being planned.

3.6.6. The Subcommittee considered that, if it works, bortezomib generally produces an extremely rapid response (within a few weeks) which was important, particularly for patients who are deteriorating rapidly. The Subcommittee considered that there is a small group of patients, particularly those with cardiac problems, for whom bortezomib treatment would be important. Members noted that response to treatment would become apparent within three cycles (continuing to six to eight cycles, if effective).

3.6.7. The Subcommittee considered that is was appropriate that PHARMAC consider a Pharmaceutical Schedule funding application for bortezomib in these patients. The Subcommittee considered that [withheld under s9(2)(a) of the OIA] was an expert in this area, [withheld under s9(2)(a) of the OIA].

3.6.8. The Subcommittee **recommended** that PHARMAC staff request a funding application from the Haematology Society. Members recommended that the submission should include, at minimum, relevant available evidence, definition of the patient group and estimate of potential patient numbers. The Subcommittee noted that the request could be directed to the Haematology Society Chairman, [withheld under s9(2)(a) of the OIA], and noted that [withheld under s9(2)(a) of the OIA]. Members considered that it would be reasonable to put a timeframe on the receipt of such an application, such that, if an application had not been received within the timeframe, new Cancer EC applications would not be approved.

3.7. Bortezomib for IgA/IgG/t(4:14 translocation) Multiple Myeloma / Plasma Cell Leukaemia

3.7.1. The Subcommittee noted that bortezomib is currently being funded under the Cancer EC scheme for a small population of patients with various genotype-specified plasma cell disorders. The Subcommittee reviewed the supporting literature supplied with the relevant Cancer EC applications.

3.7.2. The Subcommittee considered that the literature provided for review was limited; Members noted that they were aware of additional published data.

3.7.3. The Subcommittee considered that specifying patient groups, and even individuals, at a molecular level (ie by genotype) is likely to be seen more in future funding applications as more therapies are being targeted in this way.

3.7.4. The Subcommittee considered that dealing with such applications under the Cancer EC scheme was problematic since all people are, in some way, unique; however, this does not mean that all cases are exceptional. Members considered that the Cancer EC scheme was developed to deal with truly exceptional circumstance.

3.7.5. The Subcommittee considered that it was appropriate that PHARMAC consider a Pharmaceutical Schedule funding application for bortezomib in patients with various genotype-specified plasma cell disorders.

3.7.6. The Subcommittee **recommended** that PHARMAC staff request a funding application from the Haematology Society. Members recommended that the submission should include, at minimum, relevant available evidence, definition of the patient group(s) and estimate of potential patient numbers. Members considered that it would be reasonable to put a timeframe on the receipt of such an application, such that if an application had not been received within the timeframe, new Cancer EC applications would not be approved

3.8. Azacitadine for transfusion dependent Acute Myeloid Leukaemia / Myelodysplastic Syndrome

3.8.1. The Subcommittee noted that azacitadine is currently being funded under the Cancer EC scheme for a small population of patients with transfusion dependent Acute Myeloid Leukaemia or Myelodysplastic Syndrome. The Subcommittee reviewed the supporting literature supplied with the relevant Cancer EC applications.

3.8.2. The Subcommittee considered that evidence from a phase III study open-label trial (Fenaux et al Lancet Oncol 2009; 10: 223–32) demonstrated that treatment with azacitidine improved overall survival in patients with myelodysplastic syndromes compared with best supportive care.

3.8.3. The Subcommittee considered that azacitidine was now the standard of care treatment for patients with high risk myelodysplastic syndromes. The Subcommittee considered that it was appropriate that PHARMAC consider a Pharmaceutical Schedule funding application for azacitadine.

3.8.4. The Subcommittee **recommended** that PHARMAC staff request a funding application from the supplier of azacitadine. Members recommended that the submission should include, at minimum, relevant available evidence, definition of the patient group(s) and estimate of potential patient numbers. Members considered that it would be reasonable to put a timeframe on the receipt of such an application, such that if an application had not been received within the time frame, new Cancer EC applications would not be approved

3.9. Pipobroman for polycythaemia / essential thrombocythaemia

3.9.1. The Subcommittee noted that a pipobroman is currently being funded under the Cancer EC scheme for a small population of patients with polycythaemia or essential thrombocythaemia. The Subcommittee reviewed the supporting literature supplied with the relevant Cancer EC applications.

3.9.2. The Subcommittee considered that currently standard treatment in patients with polycythaemia or essential thrombocythaemia was hydroxyurea. However, members considered that a small number of patients would experience allergic reactions or treatment intolerance to hydroxyurea and pipobroman would be of particular use in these patients. Members considered that that in Europe pipobroman treatment was often used as an alternative to hydroxyurea and considered to be in a similar class with similar low potential leukaemogenic risk.

3.9.3. The Subcommittee noted that at present anagrelide is available and funded for the treatment of thrombocytosis in patients with essential thrombocythamia (or polycythaemia vera) whose disease did not respond to hydroxyurea or for those in whom hydroxyurea treatment was not appropriate.

3.9.4. The Subcommittee noted that anagrelide has significant side effects including an increased risk of haemorrhage in patients taking aspirin. Members also noted that anagrelide may be more expensive than pipobraman, and there may be possible cost-savings to the Pharmaceuticals Budget if the funding of pipobroman reduced the use of anagrelide. The Subcommittee noted that pipobroman is currently an unregistered medicine.

3.9.5. The Subcommittee **recommended** that PHARMAC staff request a funding application from the Haematology Society. Members recommended that the submission should include, at minimum, relevant available evidence, definition of the patient group(s) and estimate of potential patient numbers. Members considered that it would be reasonable to put a timeframe on the receipt of such an application, such that if an application had not been received within the time frame, new Cancer EC applications would not be approved

3.10. Rabbit anti-thymocyte globulin (ATG) for Graft Versus Host Disease (GVHD) prophylaxis

3.10.1. The Subcommittee noted that rabbit antithymocyte globulin (ATG) is currently being funded under the Cancer EC scheme for a small population of patients receiving a Matched Unrelated Donor (MUD) haematopoietic stem cell transplant (HSCT) who require Graft Versus Host Disease (GVHD) prophylaxis. The Subcommittee reviewed the supporting literature supplied with the relevant Cancer EC applications.

3.10.2. The Subcommittee considered that, although rabbit ATG was used as part of conditioning therapy for transplant, the transplant itself was for the treatment of cancer. Therefore, funding of rabbit ATG should be through the Pharmaceutical Schedule and/or Cancer EC.

3.10.3. The Subcommittee considered that the major difficulty in MUD transplant was the risk of acute or chronic GVHD. Members noted that a primary goal of GVHD prophylaxis is to reduce the number of circulating T cells prior to transplant. Members considered that a number of treatments were used to reduce circulating T cells, including alemtuzumab, ,or ATG-type molecules, for example currently funded equine ATG. However, members noted that these treatments, particularly alemtuzumab, are strongly immunosuppressive and carry an increased risk of infection.

3.10.4. The Subcommittee considered that rabbit ATG was now a standard of care treatment option for patients undergoing transplantation.

3.10.5. The Subcommittee noted that clinicians routinely switch between equine and rabbit ATG for patients requiring a second ATG treatment in settings such as aplastic anaemia. Members considered that the two products had similar efficacy but that rabbit ATG was cheaper than equine ATG. Members noted that, under the current rules of the Pharmaceutical Schedule, both of these treatments can be accessed for paediatric oncology cases. However, in adult cases, approval is required for rabbit ATG under Cancer EC because only equine ATG is listed on the Pharmaceutical Schedule.

3.10.6. The Subcommittee considered that the current trend favours rabbit ATG over equine ATG because rabbit ATG has immunological advantages and also has a lower cost.

3.10.7. The Subcommittee noted that the evidence of benefit of ATG, or other T-cell reducing treatments, for reducing GVHD was generally limited to uncontrolled studies. The Subcommittee noted that in uncontrolled studies the clinicians tend to adhere to the 'recipe' trialled, which may be a factor in these applications being submitted. The Subcommittee noted that there is currently an International Phase II study using rabbit ATG which provides the thymoglobulin at no cost.

3.10.8. The Subcommittee considered that transplant treatment was complex; therefore, assessing the specific benefit of treatment attributable to rabbit ATG as a stand alone item would be very difficult.

3.10.9. The Subcommittee **recommended** that rabbit ATG should be listed on the Pharmaceutical Schedule, mainly because it was cheaper than the current funded treatment, equine ATG. The Subcommittee further **recommended** that, until such time it was listed on the Pharmaceutical Schedule, access to this treatment should continue to be approved under Cancer EC.

4. Gemcitabine and vinorelbine for relapsed Hodgkin's disease or T-cell lymphoma

4.1. The Subcommittee considered a paper from PHARMAC staff regarding a cost effectiveness analysis of combination gemcitabine and vinorelbine for the treatment of patients with relapsed Hodgkin's disease (HD) or T-cell lymphoma.

4.2. The Subcommittee noted that at its 25 June 2009 meeting it had recommended that combination gemcitabine and vinorelbine be funded for up to 6 cycles for patients with T-cell lymphoma or patients with HD who fail to respond to second-line salvage chemotherapy or who relapse after transplantation.

Hodgkin's Disease

4.3. The Subcommittee considered that ICE (ifosfamide, carboplatin and etoposide) chemotherapy was the appropriate comparator for gemcitabine and vinorelbine in the cost-effectiveness analysis for patients with relapsed HD. Members also noted uncertainty around the clinical benefit of gemcitabine and vinorelbine compared with ICE due to the relatively weak evidence and the absence of any direct comparative clinical trial evidence with ICE.

4.4. The Subcommittee noted that the results of the cost-effectiveness analysis were very sensitive to changes in certain inputs, for example the use of G-CSF, place of ICE delivery (inpatient/outpatient), the number of cycles in each treatment arm and whether other drugs are given with vinorelbine and gemcitabine. Members considered that approximately one third of patients would currently receive ICE as an outpatient. However, in the future more patients would likely receive ICE in an outpatient setting; therefore, the Subcommittee considered that sensitivity analyses examining various rates on outpatient ICE treatment be performed.

4.5. The Subcommittee noted that some inputs into the cost-effectiveness model did not completely reflect likely clinical practice in New Zealand. For example, members considered that gemcitabine would be administered as a 30 minute infusion rather than over 3 hours, as in the model, and the types and dosing of antiemetics and

blood products may differ from those detailed in the model. However, members considered that changing these inputs would have minimal impact on the overall cost-effectiveness result.

4.6. The Subcommittee considered that, given the lack of comparative evidence, it was appropriate to assume similar efficacy in the cost-effectiveness model for both ICE and gemcitabine/vinorelbine in relapsed HD. Members noted that combination treatment with gemcitabine/vinorelbine was likely to be cost neutral or cost saving compared with ICE used in the inpatient setting; however, members noted that the cost/QALY increased significantly when compared with outpatient ICE treatment.

4.7. The Subcommittee reiterated its **recommendation** that combination treatment with gemcitabine and vinorelbine be funded for up to 6 cycles for patients with HD who fail to respond to second-line salvage chemotherapy or who relapse after transplantation (ie in the third-line setting). Members gave this recommendation a medium priority.

4.8. The relevant decision criteria for this recommendation 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 6: the budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule;*

T-cell Lymphoma

4.9. The Subcommittee considered that the treatment algorithm for T-cell lymphomas was poorly defined, principally due to the rarity and heterogeneity of different types of T-cell lymphoma and lack of randomised clinical trials to inform treatment choices.

4.10. The Subcommittee considered that in the first-line setting, the most appropriate comparator treatment for the cost-effectiveness model would be CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy. Members noted that CHOP was an inexpensive chemotherapy regimen given in the outpatient setting; however, members considered that some younger patients may receive more expensive modified CHOP regimens, e.g dose-dense CHOP, given every 14 days.

4.11. The Subcommittee considered that it was appropriate to assume similar efficacy in the cost-effectiveness model for both CHOP and gemcitabine/vinorelbine in the first line treatment of T-cell lymphoma. Members further noted that, although the adverse event profiles of CHOP compared with gemcitabine with vinorelbine were different, PHARMAC staff were unable to identify any quantifiable QALY gain (in terms of reduced toxicity) from treatment with gemcitabine/vinorelbine compared with CHOP. Members noted that, given the lack of any discernable efficacy or toxicity benefit of gemcitabine/vinorelbine compared with CHOP, and the increased cost of gemcitabine/vinorelbine compared with CHOP, the cost effectiveness of gemcitabine/vinorelbine in this setting would likely be very high. Therefore, the Subcommittee **recommended** that funding of gemcitabine/vinorelbine for the first line treatment of patients with T-cell lymphoma be declined.

4.12. The Subcommittee considered that in the relapsed T-cell lymphoma setting, the most appropriate comparators treatments for the cost-effectiveness model would be DHAP (dexamethasone, cytarabine and cisplatin) or ICE chemotherapy. Members considered that it was appropriate for the cost-effectiveness model for relapsed T-cell lymphoma to be based on the relapsed HD model with similar inputs

4.13. Members noted that the cost-effectiveness of combination treatment with gemcitabine/vinorelbine in patients with relapsed T-cell lymphoma was likely to be similar to that in the relapsed HD setting.

4.14. The Subcommittee **recommended** that combination treatment with gemcitabine and vinorelbine be funded for up to 6 cycles for patients with T-cell lymphoma who fail to respond to second-line salvage chemotherapy or who relapse after transplantation (ie in the third-line setting). Members gave this recommendation a medium priority.

4.15. The relevant decision criteria for these recommendations 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 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. Thalidomide for the treatment of patients with newly diagnosed multiple myeloma

5.1. The Subcommittee reviewed an application from Celgene Pty Ltd for the funding of thalidomide to be widened to include treatment of patients with newly diagnosed multiple myeloma. The Subcommittee noted that the application was considered by PTAC at its August 2009 meeting. The Subcommittee also considered a PHARMAC staff review of the economic analysis provided by the supplier for thalidomide in patients ineligible for stem cell transplant.

5.2. The Subcommittee noted the application comprised treatment with thalidomide for two distinct populations: stem cell transplant ineligible patients, and stem cell transplant eligible patients.

5.3. The Subcommittee noted that multiple myeloma was not curable and, therefore, treatment goals were principally to extend and/or improve quality of life. The Subcommittee considered that multiple myeloma predominantly affected older people and that approximately half of all multiple myeloma patients (approximately 150 patients per year) would be ineligible for a stem cell transplant, mainly due to their age and associated comorbidities. Members noted that the incidence of multiple myeloma and risk of death from multiple myeloma is higher in Maori compared with non-Maori.

5.4. The Subcommittee noted PTAC's recommendation that the application for stem cell transplant eligible patients be declined. The Subcommittee agreed with PTAC's view that in transplant eligible patients, interpretation of the impact of thalidomide on longer term outcome data, including overall survival, was confounded by patients

having received a transplant and subsequent (uncontrolled) treatments. Therefore, the Subcommittee considered that PTAC's recommendation was reasonable.

5.5. The Subcommittee focused its discussion on the use of thalidomide in transplant ineligible patients. Members reviewed evidence from five randomised controlled studies comparing melphalan and prednisone (MP) with and without thalidomide in stem cell transplant ineligible patients with newly diagnosed multiple myeloma. Members considered that the evidence was of relatively high quality despite some heterogeneity in the study designs; for example the populations enrolled comparator treatments and thalidomide dosing differed.

5.6. The Subcommittee considered that, overall, the evidence indicated that the addition of thalidomide to MP treatment resulted in statistically significant improvements in progression free survival and the proportion of patients with a treatment response. Members noted that in one study (IFM 99-06 Facon et al. 2007 The Lancet 370(9594): 1209-1218) thalidomide treatment was also associated with an improvement in overall survival (HR=0.59, 95%CIs 0.46-0.81, p=0.0006); however, members considered that the dosing of thalidomide in this study (average 238 mg/day, range 100 mg/day to 400 mg/day) was higher than that which would be used in New Zealand clinical practice and the duration of treatment (9.9 months) was likely shorter. Members considered that in clinical practice patients with relapsed myeloma generally receive a maximum of 200 mg/day thalidomide, with most patients receiving only 100 mg/day, for on average 13-15 months.

5.7. The Subcommittee noted that thalidomide treatment was associated with significant toxicity;l in particular it was associated with an increased risk of venous thromboembolism (VTE), peripheral neuropathy and somnolence. Members considered that approximately 50% of patients on thalidomide would experience does-related peripheral neuropathy, 5-10% somnolence and 10-20% VTE.

5.8. The Subcommittee considered that the cumulative toxic effects of thalidomide were treatment limiting. Therefore, if first-line thalidomide treatment was funded, it would likely shift thalidomide treatment from the current second/third-line setting to earlier in the multiple myeloma treatment algorithm, rather than increasing the overall duration (and therefore costs) of thalidomide treatment significantly. However, members noted that there may be increased costs associated with thalidomide treatment in the first-line setting due to the requirement for warfarin VTE prophylaxis, which may not be given in the second/third line setting (depending on whether thalidomide is used as monotherapy or combined with dexamethasone). Members considered that in the first line setting, patients would most likely receive 6 months of VTE prophylaxis with warfarin followed by aspirin, whereas in the second/third line setting about half of the patients would receive aspirin only.

5.9. The Subcommittee considered that it was appropriate in the cost-effectiveness model for thalidomide to use the Weibull method, rather than a straight-line method, of extrapolation to determine the progression-free and overall survival gains for patients receiving thalidomide. The Subcommittee considered that the model should also be updated to take into account their recommendations of likely dosing and treatment duration.

5.10. The Subcommittee **recommended** that thalidomide should be funded for the first line treatment of multiple myeloma in patients ineligible for stem cell transplantation. The Subcommittee gave this recommendation a high priority.

5.11. 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.*

6. Lenalidomide for relapsed/refractory multiple myeloma

6.1. The Subcommittee considered an application from Celgene Pty Ltd for the listing of lenalidomide (Revlimid 5 mg, 10 mg, 15 mg and 25 mg capsules) on the Pharmaceutical Schedule for the treatment of patients with relapsed/refractory multiple myeloma.

6.2. The Subcommittee noted that the application had been reviewed by PTAC at its August 2009 meeting and that PTAC recommended that the application be deferred pending a review by the Subcommittee. The Subcommittee also reviewed a letter from the supplier in response to PTAC's August 2009 minute.

6.3. The Subcommittee noted that multiple myeloma was not curable and, therefore, treatment goals were principally to extend and/or improve quality of life. The Subcommittee considered that multiple myeloma predominantly affected older people and that the incidence of multiple myeloma and risk of death from multiple myeloma is higher in Maori compared with non-Maori.

6.4. The Subcommittee noted that lenalidomide is an analogue of thalidomide and that lenalidomide is indicated, in combination with dexamethasone, for the treatment of multiple myeloma patients whose disease has progressed after one therapy. Members noted that lenalidomide was also being investigated in earlier treatment of multiple myeloma.

6.5. The Subcommittee reviewed evidence from two phase III randomised placebo controlled trials comparing lenalidomide plus dexamethasone with dexamethasone alone in patients who had received at least one prior therapy: studies MM009 (Weber, D et al. 2007, New England Journal of Medicine 357(21): 2133-42) and MM010 (Dimopoulos, M et al. 2007, New England Journal of Medicine 357(21): 2123-32). The Subcommittee noted that in these studies lenalidomide plus dexamethasone treatment was associated with improvements in progression free survival and overall survival compared with dexamethasone alone.

6.6. The Subcommittee noted that lenalidomide treatment was associated with an increased risk of venous thromboembolism, anaemia and thrombocytopaenia. Members noted that patients treated with lenalidomide and dexamethasone would require prophylactic anticoagulation therapy (low molecular weight heparin or warfarin) and a small number of patients may require transfusion.

6.7. The Subcommittee considered that treatment for relapsed/refractory multiple myeloma (either lenalidomide plus dexamethasone or dexamethasone alone) was less effective in patients who had previously been exposed to thalidomide compared with thalidomide naïve patients. Members therefore considered that lenalidomide would be most beneficial in patients who had failed one prior therapy (i.e. second-line treatment prior to thalidomide) rather than third-line treatment following thalidomide treatment.

6.8. The Subcommittee considered that the supplier's cost-effectiveness analysis may overstate the cost effectiveness of lenalidomide, because the cost per QALY result seemed too low compared with the results of cost-effectiveness analyses undertaken by NICE in the UK and PBAC in Australia, which yielded much higher values. The Subcommittee considered that the inputs for the comparator treatment arm in PHARMAC's cost-effectiveness model for lenalidomide should be consistent with that for bortezomib in relapsed/refractory multiple myeloma.

6.9. The Subcommittee **recommended** that lenalidomide should be funded for the second-line treatment of patients with relapsed/refractory multiple myeloma. Members considered that access criteria, including stopping rules, similar to those of the Australian Pharmaceutical Benefits Scheme would be appropriate. The Subcommittee gave this recommendation a low priority.

6.10. 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.*