Cancer Treatment Subcommittee of PTAC
Meeting held 13 September 2013

(minutes for web publishing)

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

The Cancer Treatment 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 13 &14 February 2014, the record of which will be available in May 2014.

Record of the Cancer Treatments Subcommittee of PTAC held at PHARMAC on 13 September 2013

1. Minutes of previous meeting

1.1. The Subcommittee reviewed the minutes of its previous meeting held on 22 March 2013.

1.2. The Subcommittee noted that it had recommended that it would be appropriate to seek and list an oral magnesium tablet preparation in Section H if possible (item 3.4). However, members noted that if it were listed it would likely be used and questioned if there was sufficient evidence for efficacy compared with IV magnesium. Therefore, the Subcommittee **recommended** that if listing oral magnesium was associated with any additional cost compared with IV magnesium PTAC should review the evidence, prior to PHARMAC making a decision**.**

1.3. The Subcommittee **recommended** that the first sentence in item 6.2 in relation to bortezomib retreatment be amended as follows (changes in bold and strikethrough):

> 6.2. The Subcommittee considered that MM was a common **haematological malignancy** ~~disease~~ and is still currently incurable.

1.4. The remainder of the minute was accepted.

2. Matters Arising and Correspondence

2.1. ***Recent PTAC and Subcommittee recommendations***

- The Subcommittee reviewed the minutes of PTAC's meetings held on 14/15 February 2013 and 9/10 May 2013.
- The Subcommittee discussed the May 2013 minute in relation to dexrazoxane for cardioprotection in chemotherapy in paediatrics.
- The Subcommittee noted that although paediatric oncology currently has an exemption from the rules of the pharmaceutical schedule, 90-95% of paediatric treatment use was in common with funded adult populations with only a few exceptions, notably, dexrazoxane and clofarabine.
- In relation to dexrazoxane the Subcommittee considered that the effect of treatment on long term cardioprotection would not become evident until long after the study periods, greater than 10 years later, therefore, the relevance of the evidence considered by PTAC was questioned. Members noted that in paediatrics, unlike adults, the mycocardium was growing, therefore

damage by chemotherapy early on in life would likely increase the rate of late complications.

- The Subcommittee agreed with PTAC's recommendations. However, some members were concerned about access for paediatric patients who were not able to be enrolled in clinical trials. However, overall members considered that insufficient evidence at this time to support its use outside of clinical trials. The Subcommittee **recommended** that Paediatric Oncologists provide further evidence for consideration of funding for patients outside of clinical trials.

2.2. ***Bendamustine***

- The Subcommittee noted an application from a clinician for the funding of bendamustine for the treatment of follicular and mantle cell lymphoma.

- The Subcommittee noted that bendamustine is registered overseas for treatment of indolent Non-Hodgkin's Lymphoma (NHL) and Chronic Lymphocytic Leukaemia (CLL) but is not currently registered in New Zealand. Members noted that the supplier had recently submitted an application for Medsafe registration. Members noted that the clinician's submission was for a narrower patient group.

- The Subcommittee noted the clinical need and enthusiasm from clinicians but considered that, whilst the evidence for bendamustine looked promising it was still was early and it may be a potentially large expense medicine. Therefore, the Subcommittee considered that it was important that it consider a full application from the supplier.

- The Subcommittee **recommended** that PHARMAC write to the clinician applicant with its view.

3. Therapeutic group review including NPPA and applications review

3.1. The Subcommittee reviewed expenditure and usage of cancer pharmaceuticals including funding applications considered under the NPPA scheme.

3.2. The Subcommittee noted that PHARMAC had granted an HML exemption for dexrazoxane for "the use of dexrazoxane in children who are enrolled in an Ethics Committee-approved clinical trial". Members noted that all of these would be Children's Oncology Group studies. However, some may enrol adolescent and young adults as well as children. Members recommended that the HML exemption be amended as follows (changes in bold and strikethrough) "the use of dexrazoxane in ~~children~~ **patients** who are enrolled in an Ethics Committee-approved **paediatric oncology** clinical trial".

3.3. The Subcommittee considered that there was an opportunity to reduce the costs associated with octreotide LAR for carcinoid syndrome. Members considered that there was a tendency for clinicians to start treatment at 30 mg and dose escalate from there as necessary, however, members **recommended** treatment be started at 20 mg, which would be sufficient in

most patients for disease control, with dose titration, up or down, in increments to 10 mg as necessary.

3.4. The Subcommittee noted NPPA applications for temozolomide for patients with relapsed Ewing Sarcoma and Rhabdomyosarcoma. Members considered this was a new standard of care for these conditions which was attractive because it was an outpatient treatment. Members **recommended** that PHARMAC seek funding applications from the clinicians who had applied under NPPA.

4. Abiraterone for prostate cancer

4.1. The Subcommittee considered an application from Janssen to list abiraterone (Zytiga) for patients with metastatic castrate-resistant prostate cancer (mCRPC). Members noted that the application comprised two populations, taxane treatment naïve, and taxane pre-treated patients as follows:

- Treatment (with concomitant prednisone or prednisolone) of patients with metastatic castration resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy ("taxane naive population")

- Treatment (with concomitant prednisone or prednisolone) of patients with metastatic castration resistant prostate cancer who have received prior chemotherapy containing a taxane ("taxane pre-treated population")

4.2. The Subcommittee noted that PTAC had considered the application at its August 2013 meeting where it recommended that abiraterone be listed on the Pharmaceutical Schedule with a low priority for taxane pre-treated patients. Members noted that PTAC had also recommended that the application be referred to the Cancer Treatments Subcommittee of PTAC (CaTSoP) for consideration and advice on appropriate Special Authority criteria, potential patient numbers, the impact on abiraterone funding on current treatment algorithms and the Subcommittee's opinion on the place of ketoconazole therapy in this indication.

4.3. The Subcommittee noted that in New Zealand some 2500 new cases present, and some 450 men die, each year of prostate cancer. Members noted that Maori and Pacific peoples are more likely to be diagnosed with advanced disease and are more likely to die of their disease even when controlling for stage (Haynes et al Soc Sci Med. 2008 Sep;67(6):928-37).

4.4. The Subcommittee noted evidence from two double blind, randomised controlled, trials in support of the application; COU-AA-301 (de Bono et al N Engl J Med 2011; 364:1995-2005 and Fizazi et al Lancet Oncol. 2012;13:983-92) comparing abiraterone versus placebo in 1095 patients who had received prior chemotherapy (taxane pre-treated population) and COU-AA-302 (Ryan et al. N Engl J Med. 2013;368:138-48) comparing abiraterone versus placebo in 1088 patients who were asymptomatic or mildly symptomatic and had not received prior chemotherapy (taxane naïve population).

4.5. The Subcommittee noted the results of two studies specifically looking at the quality of life of patients treated with abiraterone. The first study (Sternberg et al Ann Oncol. 2013 Apr;24(4):1017-25) looked at the impact of abiraterone on the fatigue associated with metastatic castration-resistant prostate cancer following docetaxel chemotherapy. The second (Harland et al Eur J Cancer. 2013 Aug: 22 (13): S0959-8049) looked at quality of life for patients with metastatic castration-resistant prostate cancer after failure of docetaxel chemotherapy.

4.6. The Subcommittee noted that Sternberg et al reported that abiraterone was associated with a significantly increased proportion of patients reporting improvement in fatigue intensity on the Brief Fatigue Inventory (58.1% versus 40.3%, P = 0.0001), improved fatigue interference (55.0% versus 38.0%, P = 0.0075), and accelerated improvement in fatigue intensity (median 59 days versus 194 days, P = 0.0155).

4.7. The Subcommittee members noted that Harland et al reported improvements in Quality of life as reported on a prostate cancer QoI scale. Members noted, total score were observed in 48% of patients receiving abiraterone versus 32% of patients receiving prednisone ($p<0.0001$). They also noted the median time to deterioration QoL score was longer ($p<0.0001$) in patients receiving abiraterone (59.9 weeks versus 36.1 weeks). Overall members considered that Harland et al and Sternberg et al offered some evidence of abiraterone favouring a QoL improvement for patients. This compared with patients receiving docetaxel or ketoconazole who may not be able to tolerate treatment.

4.8. The Subcommittee considered that there was good strength and quality of evidence for improved overall survival with abiraterone compared with placebo, in particular for the taxane pre-treated population where median overall survival was 15.8 months for abiraterone, compared with 11.2 months for placebo. Members considered whilst the data in the taxane naïve population were less mature it was likely that a greater absolute improvement would be shown in this setting when reported.

4.9. The Subcommittee noted that abiraterone has a similar mode of action to ketoconazole, inhibition of CYP17A1, with abiraterone being 100 times more potent. However, members considered that, although ketoconazole had been shown to increase time to PSA progression, it was associated with liver and gastrointestinal toxicities; therefore, its use was controversial. Members considered that there would be few patients in New Zealand being treated with ketoconazole.

4.10. The Subcommittee considered that whilst there was evidence demonstrating the docetaxel improved overall survival in mCRPC, few patients in NZ (<5%) currently received this treatment mainly owing to its toxicity. Members considered that the use of abiraterone would merely delay the use of docetaxel in this small group of patients rather than replace it, but that in the majority of patients (95%) the appropriate comparator was best supportive care.

4.11. The Subcommittee considered that limiting funding to the taxane pre-treated population as recommended by PTAC was not appropriate. Members considered that whilst the cost would be significantly constrained, the greatest benefit for abiraterone was likely to be in the taxane naïve setting.

4.12. The Subcommittee considered that the supplier's estimates of the numbers of patients who would receive abiraterone in the taxane naïve group were far too low. Members noted that, as prostate cancer patients were spread across Urology, Radiation Oncology and Medical Oncology practices, therefore, it was difficult to get a good estimate of the likely number of patients. Members considered that the majority of patients with mCRPC would receive abiraterone if it were funded, and estimated this group to be approximately 1000 patients per year. Members recommended that PHARMAC seek input from specialists in urology, radiation and medical oncology to get a better estimate of patient numbers.

4.13. The Subcommittee considered that abiraterone provided a significant advance in the treatment of prostate cancer and it would be a high priority based on evidence alone. However, members noted that abiraterone was an expensive treatment. Members noted that a discount had been provided in the UK.

4.14. The Subcommittee noted the budget impact of the proposal. They noted that while access in the post docetaxel setting would limit this impact, increased clinical benefit would be expected in the pre-docetaxel group. Members noted that some increased usage of docetaxel may occur if abiraterone funding was restricted to the taxane pre-treated group only.

4.15. The Subcommittee **recommended** that abiraterone should be funded on the Pharmaceutical Schedule for taxane naïve patients subject to the following Special Authority criteria:

> Initial Application
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> Applications only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months for applications meeting the following criteria:
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> All of the following:
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> 1. Patient has symptomatic progressive Metastatic Castration Resistant Prostate Cancer; and
> 2. Patient has not had prior treatment with cytotoxic chemotherapy; and
> 3. Patient has ECOG performance score of 0-1.
>
> Renewal Application
>
> Applications only from a relevant specialist or any other 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. No evidence of disease progression; and
> 2. No initiation of taxane chemotherapy; and
> 3. The treatment remains appropriate and the patient is benefiting from treatment.

4.16. The Subcommittee gave this recommendation a low priority. The Subcommittee noted that its priority recommendation would increase if the cost of abiraterone was reduced significantly.

4.17. 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 Maori 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.*

5. Cetuximab for head and neck squamous cell carcinoma

5.1. The Subcommittee considered an application from Merck Serono for the funding of cetuximab (Erbitux) for patients with locally advanced squamous cell cancer of the head and neck, who are considered medically unsuitable for chemotherapy treatment with cisplatin.

5.2. The Subcommittee noted that the application had been reviewed by PTAC at its May 2013 meeting where it deferred making a recommendation on cetuximab and recommended that the application be referred to CaTSoP for advice regarding **Error! Bookmark not defined.** the impact of renal impairment on the efficacy of cetuximab; the relevance of the evidence to the proposed patient group; and the patient group most likely to benefit.

5.3. The Subcommittee also reviewed further information from the supplier in response to some of the issues raised by PTAC at its May 2013 meeting and a letter of support for the application from a Radiation Oncologist.

5.4. The Subcommittee noted that head and neck cancers originate in the oral cavity, nasopharynx, hypopharynx and the larynx with the majority of head and neck cancers having squamous cell histology (HNSCC). Members noted that oral cancers are twice as common in men compared with women and that Maori are more likely to present with advanced disease and Maori males are twice as likely to die of their disease as non-Maori males.

5.5. The Subcommittee noted that tobacco and alcohol consumption, human papillomavirus (HPV) infection and lower socioeconomic group were known risk factors for the development of head and neck cancer. Members noted that the peak incidence of head and neck cancer was between the ages of 70 to 74 years and that around half of all patients present with other pulmonary, cardiac, hepatic or neurologic comorbidities. Therefore, consideration of the patient's physical condition was important when determining appropriate treatment.

5.6. The Subcommittee considered that the current standard therapy in NZ for fit patients with locally advanced HNSCC disease is cisplatin with concurrent radiation therapy (RT). However, members noted that cisplatin was contraindicated in patients with renal impairment, hearing impairment and peripheral neuropathy. Members considered that approximately 30% of patients presenting with locally advanced HNSCC would not be suitable for cisplatin treatment.

5.7. The Subcommittee noted a study comparing cisplatin and carboplatin based chemoradiation in a matched retrospective pair analysis of patients with locally advanced HNSCC (Wilkins et al. Oral Oncology Volume 49, Issue 6 , Pages 615-619, 2013), However, members considered the evidence from this study was poor with only those reporting 100% compliance enrolled. Members considered evidence for the use of oxaliplatin was insufficient to support its use in place of cisplatin.

5.8. The Subcommittee considered that very few patients, if any, would be offered carboplatin in place of cisplatin owing to the lack of evidence and its similar toxicities and contraindications. Therefore, members considered most patients with a contraindication to cisplatin would be treated with RT alone. Members considered that there would be approximately 50 patients nationally per year presenting with locally advanced HNSCC who would be treated with RT alone.

5.9. The Subcommittee noted key evidence from a randomised controlled study in 424 patients with locoregionally advanced cancers of the oropharynx, hypopharynx, or larynx comparing RT alone with RT plus weekly cetuximab at an initial dose of 400 mg/m2 administered 1 week before the start of RT, followed by 250 mg/m2 weekly for the duration of the radiation (Bonner et al. NEJM 2006; 354:567-578, updated, Bonner et al. Lancet Oncol 2010;11:21-28). The Subcommittee noted that blinding of the study participants was not possible because cetuximab treatment is associated with an acneiform rash. However, treatment outcomes were assessed by a blinded independent committee. Members noted that patients enrolled in this study did not need to have contraindications to cisplatin.

5.10. The Subcommittee noted that the median duration of locoregional control, the primary endpoint in the Bonner study, was significantly improved in patients treated with cetuximab; 24.4 months for patients treated with the combination versus 14.9 months for those treated with RT alone (hazard ratio (HR) 0.68, 95% CI 0.52-0.89, p=0.005). Members also noted that the secondary endpoint of median overall survival was significantly improved for patients treated with cetuximab; 49.0 versus 29.3 months (HR for death 0.73, 95% CI 0.56-0.95, p=0.018) with 5-year overall survival 45.6% in the cetuximab-RT group and 36.4% in the RT-alone group. Members also noted that an unplanned subgroup analysis showed that an acneform rash of grade 2 or more in patients receiving cetuximab predicted longer median overall survival; 68.8 months versus 25.6 months (HR for death 0.49, 95% CI 0.34-0.72, p=0.002).

5.11. The Subcommittee noted that there were no differences in Quality of Life (QoL) between the two arms of the Bonner study and in particular there was

no difference in the incidence of (severe) radiation dermatitis. However, members noted that severe radiation dermatitis including skin necrosis have subsequently been reported, and some authors have observed a tenfold increase of grade 3 or 4 dermatitis with cetuximab-RT when compared with RT alone (Specenier et al Biologics. 2013; 7: 77–90).

5.12. The Subcommittee noted that although the Bonner study only enrolled patients with normal renal function, however, unlike cisplatin and carboplatin, cetuximab was not renally excreted, therefore, renal impairment was not a contraindication for cetuximab use.

5.13. The Subcommittee noted a published economic analysis (Brown et al Value Health. 2008 Sep-Oct;11(5):791-9) concluded that the incremental cost per quality-adjusted life-year for patients receiving radiotherapy in combination with cetuximab compared to radiotherapy alone among all countries was in the range of 7,000 to 11,000 euros.

5.14. The Subcommittee noted that based on an unplanned subgroup analysis of the Bonner study for each of the separate Karnofsky performance-status score subgroups (Karnofsky performance-status scores of 100%, 90%, 80%, 70% and less than 70%) NICE in the UK had recommended the use of cetuximab only in patient whose Karnofsky performance-status score was 90% or greater. However, members considered this analysis to be hypothesis generating at best.

5.15. The Subcommittee considered that overall the strength and quality of the evidence for a 10 month improvement in loco-regional control and 20 month improvement in survival was good, and this was a significant result in this high health need patient group.

5.16. The Subcommittee **recommended** that cetuximab should be funded on the Pharmaceutical Schedule for use in combination with radiation therapy for patients with locally advanced, non-metastatic, squamous cell cancer of the head and neck, who have a significant renal, ototoxicity, peripheral neuropathy, or myelosuppression contraindication to both cisplatin and carboplatin. Members gave this recommendation a High priority.

5.17. 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 Maori 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.*

6. Cetuximab for metastatic colorectal cancer

6.1. The Subcommittee considered an application from Merck Serono for the funding of cetuximab (Erbitux) in combination with irinotecan-based chemotherapy for the first line neoadjuvant treatment of patients with K-RAS wild-type metastatic colorectal cancer (mCRC) whose metastases are limited to the liver.

6.2. The Subcommittee also reviewed an application from the Gastrointestinal Cancer Special Interest Group (GI-SIG) for cetuximab, monotherapy or in combination irinotecan-based chemotherapy, for the treatment of patients with K-RAS wild-type mCRC refractory to irinotecan and oxaliplatin. Members noted that the populations being requested for funding by Merck Serono and GI-SIG differed.

6.3. The Subcommittee noted that PTAC had reviewed the applications at its May 2013 meeting where it deferred making a recommendations pending review by CaTSoP.

6.4. The Subcommittee noted that the incidence of CRC in New Zealand is high by international standards and that complete resection of disease contributes to survival. Members noted in patients who present with liver metastasis, an estimated 10%–20% have potentially resectable metastases and that neoadjuvant chemotherapy (FOLFOX or FOLFIRI) followed by liver resection in these patients, together with resection of the primary tumour, will offer the opportunity for improved long-term survival and perhaps cure, with 30%–40% of patients surviving at least 4 years.

6.5. The Subcommittee noted that cetuximab was a monoclonal antibody directed against the epidermal growth factor receptor (EGFR). Members noted that a retrospective post-hoc analysis of the CRYSTAL study which investigated the efficacy of cetuximab plus irinotecan, fluorouracil, and leucovorin (FOLFIRI) as first-line treatment in patients with EGFR positive metastatic colorectal cancer (Van Cutsem et al. NEJM 2009; 360:1408-1417 and Van Cutsem et al. J Clin Oncol 2011;29:2011-2019) demonstrated a significant association between K-RAS status and treatment effect for efficacy end points. Members noted that the addition of cetuximab to FOLFIRI in patients with KRAS wild-type disease resulted in statistically significant improvements in median overall survival (23.5 v 20.0 months; HR 0.796, p=0.0093), median progression-free survival (9.9 v 8.4 months, HR 0.696, p=0.0012), and response rate (57.3% v 39.7%; OR 2.069; p<0.001) compared with FOLFIRI alone. However, the Subcommittee noted that whilst this evidence showed that KRAS mutation status was predictive for efficacy of cetuximab, members considered that the data should be treated with caution since it was a retrospective analysis and the data set was limited to those patients with available tumour blocks.

6.6. The Subcommittee considered that the May 2013 PTAC minute summarised the available evidence well and overall there was sufficient evidence to conclude that K-RAS mutation status reliably predicts for better efficacy of cetuximab in patients with EGFR positive colorectal cancer. The

Subcommittee noted that approximately 40% of patients with EGFR positive colorectal cancer have mutations in K-RAS, therefore cetuximab may be useful in approximately 60% of CRC patients.

6.7. The Subcommittee considered that the evidence to support cetuximab as a third line treatment option (as per the GI-SIG submission) was of moderate to low quality. Members considered that whilst there may be some benefit from cetuximab treatment as an end-of-line treatment in this setting it would essentially be a very expensive palliative treatment. Therefore, the Subcommittee **recommended** the application from GI-SIG for cetuximab for the treatment of patients with K-RAS wild-type mCRC refractory to irinotecan and oxaliplatin be declined.

6.8. The Subcommittee noted that in response to PTAC's May 2013 minute Merck Serono had provided relevant new evidence from two reports in support of its application. The first report was for was a randomised controlled trial of chemotherapy (FOLFOX or FOLFIRI) with or without cetuximab for up to 12 cycles (24 weeks) in 138 patients with K-RAS wild-type unresectable colorectal liver-limited metastases (Ye et al J Clinical Oncology 2013; 31(16):1931-1938). Treatment continued until tumour response indicated suitability for surgery for liver metastases or until disease progression or unacceptable toxicity. Members noted that the primary end point was the rate of patients converted to resection for liver metastases, which was assessed by a multidisciplinary team after four cycles and then every two cycles up to 12 cycles. To provide an objective assessment of changes in resectability, radiologic images were reviewed by three liver surgeons, who were blinded to the clinical data. Patients were considered to have resectable disease if at least 50% of the surgeons voted for resection. Following surgery it was advised that patients complete treatment up to a maximum of 12 cycles of chemotherapy. Secondary endpoints included tumour response, overall survival and progression-free survival. The Subcommittee considered that, whilst this was a small study it was well designed and therefore considered the strength and quality of the evidence to be good.

6.9. The Subcommittee noted that in the Ye study significantly more patients in the cetuximab arm achieved complete resection of their liver metastases (R0 25.7% v 7.4%, p=0.004) with the odds of being resected with curative intent for the cetuximab arm being more than four times greater than the control (odds ratio 4.37, p<0.01). Members noted this translated to a statistically significant improvement in median progression free survival time (10.2 v 5.8 months; hazard ratio 0.60, p=0.004), and median overall survival time (30.9 v 21.0; hazard ratio 0.54; p=0.013) with cetuximab, and at 3 years more cetuximab treated patients were alive compared with chemotherapy alone (41% v 18%).

6.10. The Subcommittee noted that EGFR and K-RAS testing were not universally publically funded in New Zealand. However, some patients were currently privately funding these tests at a cost of around $260. Members considered that suppliers estimate of the number of patients who would be treated with cetuximab was reasonable at around 180 patients in year 1. Members considered that based on the available evidence the majority of patients

would receive cetuximab in combination with irinotecan rather than oxaliplatin-based chemotherapy (FOLFIRI rather than FOLFOX).

6.11. The Subcommittee considered that whilst the studies permitted up to 12 cycles of cetuximab in combination with chemotherapy, it was likely that most patients would not receive this many cycles owing to concerns about chemotherapy, principally irinotecan, toxicities. Members considered that bi-monthly CT scans would routinely be undertaken in this population with the majority becoming resectable between 4-12 cycles.

6.12. Overall the Subcommittee considered that the evidence for benefit of cetuximab in improving cure rates for patients with EGFR positive, K-RAS wild type mCRC confined to the liver was compelling, and whilst the cost and cost effectiveness was relatively high, given that the intent of treatment was curative, it was probably acceptable. Members considered that that other markers, such as BRAF expression may help refine the patient group further in the future but that the data for these were not yet mature. Members considered that overall the evidence for cetuximab was more compelling than a previous application reviewed for treatment with neoadjuvant bevacizumab in patients with mCRC confined to the liver.

6.13. The Subcommittee **recommended** that cetuximab in combination with irinotecan-based chemotherapy should be funded for the first line neoadjuvant treatment of patients with K-RAS wild-type metastatic colorectal cancer (mCRC) whose metastases are limited to the liver. Members gave this recommendation a Medium priority.

6.14. 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 Maori 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.*

7. Lenalidomide and bortezomib for multiple myeloma

7.1. The Subcommittee considered an application from Celgene to fund lenalidomide (Velcade) for patients with multiple myeloma (MM) as a third treatment after prior treatment with bortezomib and thalidomide, and as a second line treatment for patients who have experienced significant peripheral neuropathy following treatment with bortezomib or thalidomide. Members also noted a letter from the HSANZ in support of the application.

7.2. The Subcommittee noted that MM is an incurable disease, therefore treatment aims are to delay disease progression, and extend, and/or improve quality of life. The Subcommittee noted that there are approximately 250-300 patients diagnosed each year with multiple myeloma in New Zealand, and

that patients are usually aged between their fifties and sixties when diagnosed. The Subcommittee noted that the median survival of patients with MM is approximately 8 years in younger patients and 2.5 years in patients over the age of 65.

7.3. The Subcommittee noted that there have been several applications for funding of various novel MM treatments (thalidomide, bortezomib and lenalidomide) over the last few years. The Subcommittee noted that the funding of lenalidomide has been reviewed by PTAC and CaTSoP for use in relapsed/refractory MM. In summary, PTAC recommended in February 2010 that lenalidomide be funded with low priority for second-line MM treatment but also recommended that bortezomib was preferred over lenalidomide for this patient group. Bortezomib was funded in 2011 for use in either first or second-line setting (but not both); therefore, the proposal for lenalidomide in the second-line setting was not progressed by PHARMAC. The Subcommittee also noted that thalidomide is currently funded for all MM patients with no limit on the duration of treatment or number of thalidomide treatment cycles.

7.4. The Subcommittee considered that in New Zealand, more than 50% of patients would likely receive bortezomib in the first-line setting in combination with other treatments e.g. alkylating agents and corticosteroids, with the remaining patients receiving alkylating agents and corticosteroids, commonly with thalidomide, with younger and fitter patients going on to have treatment with high dose melpahlan and autologous haematopoietic stem cell transplant. Members considered that after 2-5 years (or sooner in older patients), most patients would relapse and require further treatment with, current second-line treatment options including bortezomib (if it had not already been used first-line) or thalidomide (if bortezomib had been used first-line). The Subcommittee considered that current third-line treatment options include retreatment with thalidomide, high dose dexamethasone or experimental/ unfunded treatments including lenalidomide.

7.5. The Subcommittee also noted that it had recently reviewed an application for bortezomib retreatment at its March 2013, where it recommended funding bortezomib retreatment in patients who demonstrated a prior response lasting 12 months following a bortezomib-free period of 12 months with medium priority.

7.6. The Subcommittee noted that both bortezomib and thalidomide treatment were associated with dose limiting peripheral neuropathy therefore there was an unmet health need for an alternative treatment in this patient group.

7.7. The Subcommittee reviewed evidence from the two key phase 3, double blind randomised controlled studies, the 009 and the 010 studies (Weber D et al. NEJM 2007;357(21):2133-42 and Dimopoulos M et al. NEJM 2007;357(21):2123-32) which compared lenalidomide with placebo, both in combination with dexamethasone, in patients with relapsed refractory MM who had received at least one prior therapy. The Subcommittee noted that it had reviewed evidence from these studies in previous submissions of lenalidomide.

7.8. The Subcommittee noted pooled analysis of data from the 009 and 010 studies that demonstrated a higher overall response rate (60% vs. 20%), longer progression free survival (10 months vs. 5 months) and longer overall survival (34 months vs. 30 months) for lenalidomide plus dexamethasone compared with dexamethasone alone in patients with relapsed refractory MM.

7.9. The Subcommittee noted a multivariate analysis of the pooled results (Stadmauer EA et al. Eur J Haematol 2009;82:426-432) that showed that the patients with only one prior therapy had a significant improvement in benefit after first relapse compared with those who had received two or more prior therapies. Patients with one prior therapy had significantly prolonged median time to progression (17 vs. 11 months; P = 0.026) and progression-free survival (14 vs. 10 months, P = 0.047) compared with patients treated in later lines. Overall response rates were also higher (67% vs. 57%, P = 0.06) and overall survival was significantly prolonged (42.0 vs. 35.8 months, P = 0.041) in patients treated with only one prior therapy compared with those who had received ≥ 2 prior therapies. Members considered that the data suggest that the greatest benefit for lenalidomide occurs with earlier use.

7.10. The Subcommittee noted that there was no randomised controlled evidence comparing the use of lenalidomide with thalidomide in the third line setting, however, members considered it likely that lenalidomide would be more effective that thalidomide based on head to head evidence in the first line setting (Gay et al. Blood 2010;115:1343-1350). The Subcommittee considered that lenalidomide and bortezomib retreatment would likely have similar efficacy in the third line setting after prior bortezomib treatment based on follow-up data of responses for subsequent therapy (2nd line and third line and beyond) in patients originally enrolled in the bortezomib VISTA study (Mateos et al. J Clin Oncol 2010;28:2259-2266). Overall members considered that lenalidomide was an effective drug for the treatment of MM however it was more expensive than bortezomib and thalidomide. Members considered that if lenalidomide was funded as a third line treatment it would not replace thalidomide or other third line treatment options, rather it would delay these two subsequent lines.

7.11. The Subcommittee noted that bortezomib and thalidomide were associated with higher rates of peripheral neuropathy compared with lenalidomide, therefore the funding of lenalidomide as a second line treatment for patients who had experienced peripheral neuropathy with first line bortezomib or thalidomide had merit. However, members considered that if funded in this setting the incidence of reported first line peripheral neuropathy would increase significantly, resulting in a significant number of patients being treated with lenalidomide rather than bortezomib or thalidomide in the second line setting which would come at considerable cost.

7.12. The Subcommittee **recommended** that lenalidomide should be funded as a second line treatment option for patients who have experienced significant, persistent, intractable peripheral neuropathy following treatment with bortezomib or thalidomide with medium priority. Members considered that this patient group was hard to define and would be open to significant slippage. The Subcommittee, therefore, **recommended** that PHARMAC seek input from the Neurologists regarding the exact wording of the Special

Authority to ensure it was targeted only to those patients whose peripheral neuropathy prevented further treatment with thalidomide and/or bortezomib.

7.13. The Subcommittee **recommended** that, taking into account its higher cost and similar efficacy to bortezomib retreatment, lenalidomide should be funded as a third line treatment after prior treatment with bortezomib and thalidomide with low priority. The Subcommittee reiterated its previous **recommendation** for bortezomib retreatment in this population with medium priority.

7.14. 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.*

8. Plerixafor for stem cell mobilisation

8.1. The Subcommittee considered an application from a clinician for the inclusion of plerixafor (Mozobil) on the Hospital Medicines List (HML) for use in peripheral stem cell mobilisation. The Subcommittee noted that plerixafor is currently not Medsafe-registered in New Zealand. The Subcommittee considered that the application was very well put together.

8.2. The Subcommittee considered that stem cell mobilisations are currently done with granulocyte colony stimulating factors (G-CSF) or G-CSF plus chemotherapy like cyclophosphamide. The Subcommittee noted that most centres use filgrastim but some centres are using pegfilgrastim for mobilisation. The Subcommittee considered that currently, for patients who fail to mobilise, mobilisation is repeated with higher doses of G-CSF and chemotherapy or mobilisation is abandoned altogether. The Subcommittee noted that higher doses of G-CSF and chemotherapy expose patients to the toxic effects of the treatment.

8.3. The Subcommittee noted that stem cell mobilisations are complex, costly and time-consuming. The Subcommittee noted that an apheresis collection costs approximately $2060 per session ($1580 for apheresis, $100 for CD34+ cell measurement and $380 for quality assurance measures) and each apheresis session takes about 5 hours, which would have an impact on hospital staff resourcing.

8.4. The Subcommittee noted that plerixafor is a CXCR4 chemokine receptor antagonist that blocks the binding of stromal cell-derived factor 1α which inhibits the retention of haemopoietic stem cells in bone marrow. The Subcommittee considered that there was a range of ways to use plerixafor in clinical practice:

- Use in all mobilisations upfront;

- Use in predicted poor mobilisers before start of mobilisation for example in patients who have received extensive lines of prior chemotherapy, or widespread radiotherapy to bone marrow;

- Use pre-emptively in patients with signs of likely poor yield on mobilisation (low CD34+ levels below 10/μL as measured in peripheral blood on day 5 of G-CSF treatment or low first stem cell harvest of < 1.0×10^6 CD34+ cells/kg); or

- Use following failure of mobilisation after 1 or more attempts with G-CSF or G-CSF with chemotherapy; and

- Potentially further stratifying patients based on whether they are treated with curative intent or not.

8.5. The Subcommittee noted there was good quality evidence to support the efficacy of plerixafor in mobilising stem cells. The Subcommittee noted the results of two Phase III, prospective, double blind, placebo controlled studies by DiPersio et al (J Clin Oncol 2009 Oct 1;27(28): 4767-73 and Blood 2009 Jun 4; 113(23): 5720-6).

8.6. The Subcommittee noted that plerixafor resulted in a greater proportion of non-Hodgkin's lymphoma patients (59% versus 20%, $p<0.001$) in whom $\geq5\times10^6$ CD34+ cells/kg were collected in 4 or fewer apheresis days (DiPersio et al. J Clin Oncol 2009 Oct 1;27(28): 4767-73). The Subcommittee also noted that in patients with multiple myeloma, plerixafor resulted in a greater percentage of patients (71.6% versus 34.4%, $p<0.001$) in whom $\geq6\times10^6$ CD34+ cells/kg were collected in less than or equal to 2 aphereses (DiPersio et al. Blood 2009 Jun 4; 113(23): 5720-6). The Subcommittee considered that these two studies support that plerixafor was a more efficient drug than G-CSF in generating large cell yield during mobilisations. The Subcommittee noted however that these studies were not relevant to the clinical situation in New Zealand where plerixafor would not be used upfront for all patients.

8.7. The Subcommittee noted that the Hübel et al study (Bone Marrow Transplant. 2011 Aug;46(8):1045-52) is potentially most relevant to the New Zealand setting because it reflects clinical practice here although it was a retrospective study. Plerixafor was used in patients with Non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (HL) and multiple myeloma (MM) who had previously failed mobilisation or collection or who, according to the treating physician, would not be able to provide enough stem cells based on the measurements of CD34+ cells in peripheral blood during mobilisation. The Subcommittee noted that this study defined a failed mobilisation attempt as either:

- A CD34+ cell value below 10/μL measured in peripheral blood before apheresis; or

- A pooled cell harvest of below 2.0×10^6 CD34+ cells/kg in a maximum of 7 apheresis sessions after mobilisation with G-CSF alone or in combination with chemotherapy.

8.8. The Subcommittee noted that in the Hübel et al study, a successful mobilisation was defined as a total collection of ≥2.0×10^6 CD34+ cells/kg and that 81.6% MM patients, 64.8% NHL patients and 81.5% HL patients achieved successful mobilisation with plerixafor. The Subcommittee noted that the findings of this study was consistent with a similar study in the United States (Shaughnessy et al. Bone Marrow Transplant. 2013 Jun;48(6):777-81).

8.9. The Subcommittee noted that several studies used plerixafor in a pre-emptive manner in patients predicted to mobilise poorly based on certain pre-defined criteria for example:

- low CD34+ levels below 10/μL as measured in peripheral blood on day 5 of G-CSF treatment where plerixafor is then given with a collection done on Day 6; or

- low first stem cell harvest of < 1.0×10^6 CD34+ cells/kg where plerixafor is then given and a collection done the next day.

8.10. The Subcommittee noted that Abhyankar et al (Bone Marrow Transplantation 2012; 47: 483–487) showed that out of 159 patients, 35% (55 patients) were found to be at risk of being poor mobilisers and received plerixafor. Of the 159 patients in the study, 151 (95%) were able to achieve successful mobilisation on the first attempt within a median of 1.7 days. The Subcommittee noted that of the 8 who failed initial mobilisation, 5 successfully underwent re-mobilization with plerixafor and G-CSF and 3 (1.9%) were mobilisation failures.

8.11. The Subcommittee noted that the most common adverse events associated with plerixafor in combination with G-CSF were gastrointestinal toxicities and injection site erythema (DiPersio et al. J Clin Oncol 2009 Oct 1;27(28): 4767-73 and DiPersio et al. Blood 2009 Jun 4; 113(23): 5720-6). The Subcommittee noted that nearly all adverse events noted were mild to moderate in intensity and of short duration. Up to 37% and 34% of patients treated with the combination of plerixafor and G-CSF have reported diarrhoea and nausea, when compared with 17% and 22% in the G-CSF and placebo arm, respectively. The Subcommittee noted that two patients in the plerixafor arm experienced serious adverse events, including one patient with hypotension and dizziness after plerixafor administration and one patient with thrombocytopenia after apheresis. The Subcommittee also noted that plerixafor was discontinued in three NHL patients due to a generalized seizure, systemic reactions not specified, and a central venous catheter-associated infection but all patients, however, remained in the study. The Subcommittee noted that leukocytosis, thrombocytopenia, tumour cell mobilisation, splenic enlargement, and very rarely, splenic rupture has been reported with plerixafor (Australian Product Information).

8.12. The Subcommittee noted that plerixafor was a treatment which was easier to use than persisting with ongoing doses of G-CSF and more efficient but it was also significantly more expensive. The Subcommittee noted however that there was a lack of data looking at long term outcomes following mobilisation with plerixafor.

8.13. The Subcommittee noted it would be more appropriate to assume that patients would receive 2 to 3 doses of plerixafor although the Australian Product Information indicates that 2 to 4 doses are commonly administered. The Subcommittee considered that there were 127 autologous stem cell transplants in New Zealand in 2011 (Australian Bone Marrow Transplant Recipient Registry Annual Data Summary 2011).

8.14. The Subcommittee considered that based on the clinical evidence and taking into account the higher cost of plerixafor compared to currently available treatment options, it would be appropriate to use plerixafor in a pre-emptive way and target plerixafor to patients at high risk of mobilisation failure. The Subcommittee considered that access criteria need to defined well to prevent usage creep given plerixafor is so much easier to use than current treatments. The Subcommittee considered that for the purpose of this funding application for plerixafor, it was appropriate to define 'high risk of mobilisation failure' as:

- a failure to collect $>2\times10^6$ CD34 cells/kg after 4 apheresis procedures; or
- a CD34 cell count of ≤ 10/ μL as measured in peripheral blood on day 8 of G-CSF treatment if mobilisation by G-CSF alone; or
- a CD34 cell count of ≤ 10/ μL as measured in peripheral blood on day 13 of chemotherapy with G-CSF mobilisation.

8.15. The Subcommittee noted that the definitions above are more stringent than reported elsewhere but considered that in view of the high cost of plerixafor, it would be appropriate to restrict its use to those patients with greatest clinical need.

8.16. The Subcommittee considered that the mobilisation failure rate in New Zealand was approximately 5 to 10% which was lower than in other countries. Based on these assumptions, it was reasonable to assume that 12 patients would access plerixafor in New Zealand if restricted to those at high risk of mobilisation failure.

8.17. The Subcommittee **recommended** that plerixafor should be funded in DHB hospitals with high priority subject to the following restriction criteria:

Plerixafor
Restricted
Autologous stem cell transplant – haematologist
All of the following:
1. Patient is to undergo an autologous stem cell transplant; and
2. A maximum of 4 doses of plerixafor would be used; and
3. Either:
   3.1. Efforts to collect $>2\times10^6$ CD34 cells/kg have failed after 4 apheresis procedures; or
   3.2. Apheresis has not commenced or has been discontinued because of a suboptimal blood CD34 cell count including a CD34 cell count of ≤ 10/ μL as measured in peripheral blood on day 8 of G-CSF treatment if mobilisation by G-CSF alone; or

3.3. Apheresis has not commenced or has been discontinued because of a suboptimal blood CD34 cell count including a CD34 cell count of ≤ 10/ µL as measured in peripheral blood on day 12 of chemotherapy with G-CSF mobilisation.

8.18. 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.*

9. Sorafenib for hepatocellular carcinoma

9.1. The Subcommittee considered a resubmission from Bayer New Zealand Ltd for the funding of sorafenib tosylate (Nexavar) on the Pharmaceutical Schedule for the treatment of patients with inoperable advanced hepatocellular carcinoma (HCC) with preserved liver function (Child Pugh score 5-6).

9.2. The Subcommittee noted that it, PTAC and the Gastrointestinal Subcommittee had previously reviewed the funding of sorafenib for various patient groups with advanced, inoperable, hepatocellular carcinoma (HCC). Members noted that PTAC recommended that these previous applications be declined.

9.3. The Subcommittee considered new evidence provided by the supplier based on a subgroup analysis of the pivotal phase III SHARP study (Bruix, J. et al., 2012. J Hepatol, Volume 57, pp. 821-829). Members noted that the supplier had also provided an updated cost utility analysis based on this patient group and a revised commercial proposal for sorafenib.

9.4. The Subcommittee acknowledged that whilst it was a relatively rare cancer, there was a high incididence of HCC in NZ compared with other western countries and there was a high unmet need for effective treatments for patients advanced inoperable HCC, particularly in Maori.

9.5. The Subcommittee noted that the Bruix study was an exploratory post hoc subgroup analysis of the SHARP data that demonstrated that sorafenib consistently improved median Overall Survival and Disease Control Rate compared with placebo in patients with advanced HCC, irrespective of disease etiology (HCV, HBV, alcohol), baseline tumour burden, performance status, tumour stage (B, C/D), and prior therapy (curative treatment, TACE).

9.6. The Subcommittee reiterated its previous view that, overall, the evidence demonstrated that sorefanib did provide a small overall, and progression free survival gain for patients with advanced inoperable HCC with preserved liver function. However, members considered that this benefit was not clinically

meaningful and it remained a relatively expensive treatment, given the limited benefit demonstrated. The Subcommittee reiterated its previous **recommendation** that the application be declined.

9.7. The Decision Criteria particularly relevant to these recommendations are: *(i) The health needs of all eligible people within New Zealand; (ii) The particular health needs of Maori 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.*

10. Nab-paclitaxel for breast cancer

10.1. The Subcommittee considered an application from the New Zealand Breast Cancer Special Interest Group (NZBSIG) for the funding of nanoparticle albumin-bound (nab)-paclitaxel (Abraxane) on the Pharmaceutical Schedule for the treatment of metastatic breast cancer.

10.2. The Subcommittee noted that it, and PTAC, had previously reviewed a funding application from the supplier for nab-paclitaxel in metastatic breast cancer after failure of prior therapy including an anthracycline, members noted that PTAC recommended that nab-paclitaxel be funded for this patient group only if cost-neutral to weekly paclitaxel and 3-weekly docetaxel.

10.3. The Subcommittee noted that this current application was for all patients with metastatic breast cancer indicated for a taxane (preferred option); but particularly for patients with a history of an anaphylactoid reaction to the standard paclitaxel preparation due to the cremaphor EL, the formulation vehicle in the preparation; and patients with contraindications to the pre-medications required for standard taxanes e.g. patients with diabetes in whom glucose control can be significantly destabilised by high dose corticosteroids.

10.4. The Subcommittee noted that this new application from NZBSIG was reviewed by PTAC at its May 2013 meeting where it recommended that nab-paclitaxel be funded with a low priority for patients with metastatic breast cancer and referred to CaTSoP for further advice on specific items.

10.5. The Subcommittee noted that standard taxane preparations, docetaxel and paclitaxel, have poor solubility therefore formulations contain tween and cremophor to increase solubility and enable parenteral administered. Members noted that these contributed to some of the main toxicities seen with taxanes including anaphylactoid (hypersensitivity) reactions, oedema and peripheral neuropathy. Therefore patients receiving 3 weekly taxanes routinely received pre-medicatation with glucocorticosteroids and antihistamines to limit the severity of these toxicities. However, members

noted that premedication was not routinely administered to patients receiving weekly paclitaxel because the lower dose used was rarely associated with hypersensitivity reactions and, therefore, weekly administration was now the preferred regimen for this agent.

10.6. The Subcommittee noted the nab-paclitaxel formulation does not contain Cremophor and therefore premedication with corticosteroids and antihistamines is not necessary. Members also noted that nab paclitaxel can also be reconstituted in a much smaller volume of normal saline compared with paclitaxel, and can be infused over a shorter period of time (30 minutes) compared with standard 3 hour 3-weekly infusion durations of paclitaxel. However, members noted that weekly paclitaxel was routinely administered over 1 hour.

10.7. The Subcommittee reviewed evidence for nab-paclitaxel from several studies provided, most of which it had reviewed on previous occasions. Members considered that overall the evidence demonstrated that nab-paclitaxel 260 mg/m^2 administered every three weeks was at least as effective as docetaxel 100 mg/m^2 administered every three weeks or paclitaxel 175 mg/m^2 administered every three weeks.

10.8. The Subcommittee considered that 3 weekly paclitaxel was rarely used anymore as weekly paclitaxel was more efficacious and less toxic than 3 weekly paclitaxel and was not associated with hypersensitivity reactions. Members considered that there was no advantage for nab-paclitaxel compared with weekly paclitaxel.

10.9. The Subcommittee **recommended** that nab-paclitaxel should be funded on the Pharmaceutical Schedule for the treatment of patients with metastatic breast cancer only if cost neutral to weekly paclitaxel taking into account pharmaceutical and administration costs.

10.10. The Decision Criteria particularly relevant to these recommendations are: (i) T*he 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.*