Cancer Treatments Subcommittee of PTAC
Meeting held 22 March 2013

(minutes for web publishing)

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Note:

- that this document is not necessarily a complete record of the Cancer Treatments Subcommittee meeting; only the relevant portions of the minutes relating to Cancer Treatments Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

The Cancer Treatments Subcommittee may:

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

These Subcommittee minutes were reviewed by PTAC at its meeting on 1 & 2 August 2013, the record of which will be available in October 2013.

Record of the Cancer Treatments Subcommittee of PTAC held at PHARMAC on 22 March 2013

1. Matters arising and correspondence

1.1. Correspondence regarding lapatinib

The Subcommittee reviewed correspondence from the Glaxo Smith Kline, Breast Cancer Aotearoa Coalition (BCAC) and from a clinician on behalf of the NZ Breast Cancer Special Interest Group regarding lapatinib funding as second-line treatment for patients with metastatic HER-2 positive breast cancer, particularly in patients who develop brain metastases. The Subcommittee acknowledged that there is a clinical need for a treatment in that clinical setting. However, the Subcommittee considered that there is currently insufficient evidence to support the efficacy of lapatinib in this setting. The Subcommittee maintained its previous recommendation that the application to fund lapatinib in the second line setting for patients with HER-2 positive metastatic breast cancer be declined. The Subcommittee considered that it would review its recommendation if new evidence becomes available for the use of lapatinib in this setting. The Subcommittee recommended that PHARMAC staff draft a letter to the clinician detailing the Subcommittee's discussion and recommendation.

1.2. Hospital medicines list

1.3. Members noted that there were concerns regarding the lack of availability of an oral magnesium preparation as opposed to the magnesium hydroxide paste which is compounded into oral solution currently. The Subcommittee **recommended** that it would be appropriate to seek and list an oral magnesium tablet preparation in Section H if possible.

1.4. The Subcommittee **recommended** that carboxypeptidase G2 be included on the HML and be restricted for use in the reversal of methotrexate overdose where other available treatments including folinic acid rescue with diuresis have been unsuccessful. Members noted that adequate hydration of patients prior to infusion of intravenous high dose methotrexate is also important to prevent methotrexate toxicity. The Subcommittee noted that carboxypeptidase G2 was an expensive treatment and is used very rarely, to the extent that it normally expires on the shelf but when it is needed it is normally required immediately. The Subcommittee noted that this treatment is currently stocked at Auckland city Hospital.

1.5. The Subcommittee considered that there is good clinical evidence to support the use of crisantaspase in the second-line setting for patients who are allergic to L-asparaginase and pegaspargase, Members also noted crisantaspase is used in ALL relapse protocols where treatment is with curative intent. Members considered that although 10-20% of patients with ALL relapse, very few of them receive further treatment with curative intent. The Subcommittee noted that it would be used in both adult and paediatric patients. The Subcommittee **recommended** that crisantaspase or Erwinia L-Asparaginase be included on the HML and be restricted by the following criteria:

CRISANTASPASE

Initiation – haematologist and oncologist

Any of the following:
Either:

1. Patient has acute lymphocytic leukaemia and is allergic to either L-asparaginase or pegaspargase; or
2. Patient has relapsed acute lymphocytic leukaemia as defined in a specified relapse protocol with curative intent.

2. Therapeutic group review including NPPA and applications review

2.1. The Subcommittee noted that PHARMAC had received a number of Named Patient Pharmaceutical Assessment (NPPA) applications for teniposide for the treatment of multiple myeloma, all from a single DHB. The Subcommittee noted that it has been used historically in that indication but it is not standard treatment currently. Members noted that the evidence for its use in multiple myeloma is not well established. The Subcommittee recommended that PHARMAC seek a funding application for teniposide from theDHB clinicians who had submitted NPPA applications for individual patients. If no applications were available from clinicians, the Subcommittee recommended that PHARMAC seek a funding application from HSANZ.

2.2. The Subcommittee noted a small number of NPPA applications for streptozocin for neuroendocrine tumours. Members noted streptozocin is a well-established treatment for this indication and recommended that PHARMAC seek a funding application from one of the clinicians who submitted the NPPA applications.

2.3. Members noted that PHARMAC had received NPPA applications for sunitinib in pancreatic neuroendrocrine tumours and the Subcommittee recommended that PHARMAC seek a funding application from the Gastrointestinal Special Interest Group (GISIG).

2.4. The Subcommittee noted two NPPA applications for clofarabine to treat acute myeloid leukemia, which is an unregistered indication. The Subcommittee noted that clofarabine was used in patients who could not tolerate high dose cytarabine as a result of neurological toxicity. Members noted that it was likely that there would be an increase in requests for clofarabine in the future because high dose cytarabine is increasingly being given to older patients who are more likely to have renal impairment leading to cytarabine toxicity. The Subcommittee noted that toxicity occurs in up to 8% of patients who are treated with cytarabine. Members noted that cytarabine dose reduction in renal impairment is frequently not an option because it is not advocated in AML treatment protocols. The Subcommittee noted also that clofarabine is increasingly being used in clinical trials and is also used in relapsed acute lymphocytic leukaemia (ALL) patients as a bridge to transplant. Members noted that it is an expensive treatment and recommended that a funding application be sought from HSANZ. The Subcommittee considered that the intolerance to cytarabine should be defined specifically if clofarabine is funded and that funded clofarabine should be used only in patients treated with curative intent.

2.5. The Subcommittee recommended that PHARMAC request a funding application from the supplier of lenalidomide for its use in 5q del myelodysplastic syndrome, which is a registered indication. Members noted that PHARMAC has received a number of NPPA applications for its use in this indication.

3. Oral mucositis treatment following chemoradiotherapy for head and neck cancers – calcium phosphate mouthwash and benzydamine solution

3.1. The Subcommittee reviewed a PHARMAC-initiated application for the funding of calcium phosphate mouthwash and for the full subsidisation of benzydamine, both for oral mucositis caused by chemotherapy or radiotherapy for head and neck cancers.

3.2. The Subcommittee noted that oral mucositis is a common side effect in chemoradiation therapy. It is especially common in bone marrow transplant (BMT) and in head and neck radiation treatments, where nearly all patients will experience it. The Subcommittee noted that in BMT, oral mucositis usually begins 5-10 days after initiation of chemotherapy and lasts 7-14 days, while in head and neck treatment; it usually starts 2 weeks after the first dose and lasts several months. The Subcommittee note that mucositis can affect all areas of the gastrointestinal tract and is not only limited the oral cavity. The Committee noted that the new agent for consideration was supersaturated calcium phosphate mouthwash and that the mechanism of action was unclear but thought to be related to salivary flow. The Committee noted that the product was not currently registered in New Zealand.

3.3. The Subcommittee noted that two recent Cochrane reviews related to treatments and prevention of oral mucositis did not include supersaturated calcium phosphate mouthwash (Caphosol).

3.4. The Subcommittee noted one small randomised controlled trial relating to supersaturated calcium phosphate mouthwash in mucositis (Papas et al. BMT 2003;31:705-712). The Subcommittee noted that this was a double blind prospective randomised study involving 95 patients undergoing haematopoietic stem cell transplantation (HSCT) which compared one group who received rinses and four topical 1% fluoride gel treatments administered prior to HSCT and a control group who received aqueous 0.01% sodium fluoride rinse, and four topical treatments with a placebo gel. The authors reported statistically significant decreases in the number of days of mucositis (3.72 vs 7.67, p=0.0001), duration of pain (2.86 vs 7.67, p=0.0001) doses of morphine (34.54 mg vs 122.78 mg, no p-value given), days of morphine (mean 1.02 vs mean 4.02, p=0.0001) and the days of the onset of engraftment ANC>200 mm^3 (11.12 vs 12.56, no p-value given) in the Caphosol and fluoride treatment group vs fluoride rinse group respectively. The Subcommittee noted that the trial was based at a single centre and had a limited number of patients.

3.5. The Subcommittee noted other clinical papers which considered the efficacy of supersaturated calcium phosphate mouthwash. The Subcommittee noted a study by Stockman et al (Int J Dent Hyg. 2012 Aug;10(3):175-80) who studied patients with oral malignancies treated with chemoradiotherapy. Fifty-two patients were analysed: 25 in the supersaturated calcium phosphate mouthwash group, 11 in the control group and 16 in the historical group. There was no significant difference between the supersaturated calcium phosphate mouthwash group and control group on development and severity of oral mucositis.

3.6. The Subcommittee noted a study by Jarfaut et al (EJHP 2011;17) who studied sixteen patients receiving high-dose melphalan alone (eight patients) or in combination (BEAM regimen, eight patients). In both groups, they were randomised to receive either Caphosol in addition to the standard protocol (mouth rinse based on chlorhexidine then fluconazole oral suspension) or

standard protocol alone. The incidence of mucositis appeared similar in Caphosol and control groups and all monitored parameters were not significantly different: degree of mucositis (3.5 [2.5;4] in Caphosol group vs 2 [2;2.25] in control group, p = 0.25), duration of mucositis (8.5 ± 2.3 in Caphosol group vs 7 ± 1.2 days in control group, p = 0.7), level of pain(3.3 ± 0.9 in Caphosol group vs 2.7 ± 0.65 in control group, p = 0.86; scale from 0 to 10), number of patients treated with opioid (3/4 in Caphosol group vs 1/4 in control group) and duration of this opioid treatment (7.3 days in Caphosol group vs 8 in control group, p = 0.34). Severity and duration of chemotherapy-induced mucositis were not decreased by Caphosol.

3.7. The Subcommittee noted a study by Haas et al (Oncol Nurs Forum 2008;35:505-6). This was an open labelled observational study that reported a low incidence of mucositis. The Subcommittee noted that there was no control group, no definition of tumour type and treatment site and limited assessment points (weeks 3 and 8).

3.8. The Subcommittee considered the overall level of the evidence for calcium phosphate mouthwash to be poor for use in chemoradiotherapy., With limited patient numbers in the single RCT for its use in HSCT, and the other evidence from studies with poor design that were inadequately powered, its use could not be recommended currently.

3.9. The Subcommittee noted that lignocaine solution was currently available for use in this indication. The Subcommittee considered that there was unlikely to be any cost savings from reduction in the use of PEG tubes if calcium phosphate mouthwash was funded. The Subcommittee noted that, in head and neck radiotherapy, PEG tubes are often inserted before starting the radiotherapy, meaning that any change in oral mucositis would not be seen until after the cost had been incurred. The Subcommittee also did not expect to see any reduction in length of hospital stays. The Subcommittee noted there may be a reduction in analgesia use but this would only be a small cost offset.

3.10. The Subcommittee noted that benzydamine solution was currently listed on the Pharmaceutical Schedule, and that the product was listed without Special Authority restriction but patients were required to pay a part-charge.

3.11. The Subcommittee noted two Cochrane reviews that considered multiple treatment options for the prevention and treatment of oral mucositis, both of which discussed benzydamine. Members noted that these reviews stated benzydamine had weak unreliable evidence that it would prevent mucositis, but a statistically significant difference between benzydamine and placebo in treating oral mucositis was observed.

3.12. The Subcommittee noted that benzydamine has been in clinical use for years with observed benefit, although the part-charge limits its use. The Subcommittee considered that while benzydamine is currently open listed, it would be appropriate to fully subsidise it for patients with oral mucositis as a result of treatment for cancer, and retain all other indications at the current partial subsidy.

3.13. The Subcommittee **recommended** that funding of calcium phosphate mouthwash be declined**.**

3.14. The Subcommittee **recommended** that benzydamine solution be fully subsidised for the treatment of patients with oral mucositis as a result of treatment for cancer with a low priority.

4. Bortezomib retreatment for multiple myeloma

4.1. The Subcommittee reviewed an application from the supplier for the funding of bortezomib retreatment in patients with multiple myeloma (MM) who have relapsed after a good response (complete or partial response) to prior bortezomib treatment, including patients who had received prior bortezomib treatment in either the treatment naïve or relapsed/refractory setting.

4.2. The Subcommittee considered that MM was a common disease and is still currently incurable. Current treatment in New Zealand would depend on the age of the patient and eligibility for peripheral blood stem cell or bone marrow transplantation. The Subcommittee noted that in New Zealand, more than 50% of patients would likely receive bortezomib in the first-line setting in combination with other treatments for e.g alkylating agents and corticosteroids.. Others would receive thalidomide. Members noted that after 2-3 years (or sooner in older patients), these patients would relapse and require further treatment. Current second-line treatment options would be bortezomib (if it had not already been used first-line) or other regimens typically including 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 like lenalidomide. 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.

4.3. The Subcommittee noted that there are no randomised controlled trials of bortezomib retreatment in multiple myeloma, and that the supplier had provided evidence from a number of prospective and retrospective cohort studies.

4.4. The Subcommittee noted that the supplier had provided key evidence from four studies. The Subcommittee discussed the RETRIEVE study (Petrucci, et al 2013, British Journal of Haematology; 160: 649–659) This was a phase 2, single arm study of bortezomib retreatment in 130 MM patients who had previously responded to bortezomib therapy (alone or in combination) and had had a treatment free period of ≥ 6 months. Patients received bortezomib (1.0-1.3 mg/m^2) on days 1, 4, 8 and 11 for up to eight 21-day cycles, either alone or in combination with dexamethasone at the investigators discretion. Patients had received a median of 2 prior therapies (range 1-≥4), 72% received a median of 7 cycles of bortezomib and concomitant dexamethasone was administered in 72% of patients. The overall response rate (ORR) [CR plus PR] to retreatment was 40%. In patients who achieved CR or PR to initial bortezomib treatment, ORRs for bortezomib retreatment were 63% and 52% respectively. 98% of patients experienced an adverse event, with 32% experiencing a serious adverse event.

4.5. The Subcommittee discussed the APEX study (N Engl J Med. 2005 Jun 16;352(24):2487-98) which was a randomised, open-label, phase III trial which randomized 669 patients with relapsed multiple myeloma after one to three previous therapies. The patients with progressive disease after one to three treatments were randomised to receive bortezomib (n=333) or high-dose dexamethasone (n=336). Results of the APEX study and the APEX follow-up data (Blood. 2007 Nov 15;110(10):3557-60) demonstrated that after a median follow-up of 22 months, median time to progression increased by approximately 3 months and overall survival increased by 6 months with bortezomib compared with dexamethasone. The ORR (CR plus PR) to bortezomib was 38% compared with 18% for dexamethasone. In patients who had only received one line of prior

therapy, ORRs were 45% and 26% respectively, compared with 34% and 13% respectively in those that had received more than one line of prior therapy. The Subcommittee noted that this study showed a response rate of 40-50% when bortezomib is used second line, which is similar to lenalidomide and thalidomide.

4.6. The Subcommittee considered bortezomib to be moderately effective in this setting with the evidence being of medium strength and poor quality. The Subcommittee considered thalidomide to be an appropriate comparator to bortezomib in this setting. The Subcommittee considered that there is insufficient evidence to demonstrate that bortezomib is more effective than thalidomide in the second-line setting. The benefit of bortezomib retreatment is that it would increase treatment options for patients with thalidomide being an option for third-line use in these patients. The Subcommittee considered that bortezomib retreatment would be an additional line of treatment in the multiple myeloma treatment algorithm rather than replacing existing treatment lines.

4.7. The Subcommittee acknowledged that the benefit from bortezomib retreatment in terms of overall survival and increased time to progression would be hard to quantify given the lack of evidence for its use in this setting. The Subcommittee noted that the clinical gains would progressively reduce with each line of therapy.

4.8. The Subcommittee considered that if funded for this setting, the Special Authority criteria would need to be worded carefully to prevent bortezomib from being used more than twice. The Subcommittee noted that the current criteria for bortezomib only define the funded amount of treatment as ‘cycles’ which can be interpreted very subjectively. Members noted that it would be appropriate to specifically define that one cycle of treatment is equivalent to four injections or doses of bortezomib in the Special Authority criteria. The Subcommittee also noted that it would be appropriate to require patients to demonstrate at least a partial response after 16 injections or doses to qualify for further bortezomib treatment.

4.9. The Subcommittee **recommended** that funded access to bortezomib is widened to include bortezomib retreatment with medium priority. The Subcommittee recommended that the bortezomib Special Authority be amended to include the following requirements:

- Patients would need to have demonstrated a response lasting 12 months after the previous line of therapy and have a bortezomib-free period of 12 months.
- Bortezomib retreatment is limited to 8 cycles, and each cycle comprises 4 doses.
- Patients would need to have demonstrated at least a partial response to bortezomib retreatment after 16 doses before qualifying for the further 16 doses.

4.10. 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; (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. Long acting octreotide for metastatic or unresectable SI-NETs without carcinoid syndrome

5.1. The Subcommittee reviewed an application from a group of oncologists for the funding of long-acting octreotide (octreotide LAR) for tumour control until progression in patients with metastatic or unresectable small intestinal neuroendocrine tumours (SI-NETs) without carcinoid syndrome.

5.2. The Subcommittee noted that octreotide LAR is currently funded for the patient group with carcinoid syndrome and that short acting octreotide is funded without restriction.

5.3. The Subcommittee noted the February 2013 PTAC minutes and PTAC's request that the Subcommittee advise on any health related quality of life benefit from using octreotide LAR in SI-NET patients without carcinoid syndrome and the viability of using short acting octreotide.

5.4. The Subcommittee noted one randomised controlled trial of octreotide LAR, the PROMID study (Rinke et al. J Clin Oncol. 2009;27(28):4656). Members considered the methodology to be good but that patients included people with and without carcinoid syndrome. The median time to tumour progression was 14.3 months on octreotide LAR and 6 months on placebo (hazard ratio 0.34; 95% CI, 0.20 to 0.59; p=0.000072). There was no evidence of overall survival benefit and no difference in quality of life for patients on octreotide LAR compared to placebo.

5.5. The Subcommittee noted a number of uncontrolled studies and case reports. Members noted there was no evidence of survival gain and that further evidence was unlikely to accrue, due to small patient numbers and the long natural history of the condition. Members considered that there was no improvement in quality of life for patients without carcinoid syndrome treated with octreotide.

5.6. The Subcommittee noted that short acting octreotide is currently available for use in this patient group and if patients develop carcinoid syndrome octreotide LAR is available for symptom relief. Members considered that the use of three daily subcutaneous injections of the short acting octreotide could have a detrimental effect on a patient's quality of life. However, the Subcommittee considered the overall level of the evidence for the use of long-acting octreotide in this setting to be low to moderate. The Subcommittee considered octreotide LAR was an expensive treatment for uncertain benefits.

5.7. The Subcommittee **recommended** that the application be declined.

5.8. The Decision Criteria particularly relevant to this recommendation are: (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; (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. Dexrazoxane for cardioprotection in conjunction with anthracycline chemotherapy in children and young adults

6.1. The Subcommittee reviewed an application from the National Children Cancer Network for the funding of dexrazoxane for cardioprotection in conjunction with anthracycline chemotherapy in children and young adults.

6.2. The Subcommittee noted that dexrazoxane is a drug which has been available for use for 30 years. The Subcommittee noted that most of the studies related to the drug were performed in an era prior to the current setting of safer (less cardiotoxic) anthracycline regimens.

6.3. The Committee noted that while anthracycline cardiotoxicity was a significant problem 20-30 years ago, the problem has decreased, partly due to the use of shorter courses of anthracycline. The Committee noted the protective effect of dexrazoxane against subsequent heart failure was reportedly about 70%, based on a Cochrane systematic review (van Dalen E et al. Cochrane Database of Systematic Reviews, Issue 6 Art No:CD003917) which showed a statistically significant benefit in favour of dexrazoxane for the occurrence of heart failure with a relative risk of 0.29 (95% CI 0.20 to 0.41).

6.4. The Subcommittee noted that there have been concerns about the possibility that dexrazoxane may interfere with cancer treatment (Swain et al. J Clin Oncol 1997; 15:1318) but the Subcommittee considered that there is insufficient evidence to support this. The Subcommittee noted that there have been reports of increase in the incidence of second primary malignancies, particularly acute myeloid leukaemia and myelodysplastic syndrome in dexrazoxane-treated children compared with controls (Tebbi et al. J Clin Oncol 2007;25:493–500; Salzer et al. Leukemia 2010;24:355-70). The Subcommittee noted an increased risk of other toxicities compared with controls, including severe myelosuppression and severe infection (Schwartz et al. Blood 2009;114:2051–59).

6.5. The Subcommittee considered that overall, there was good evidence to support the efficacy of dexrazoxane, with multiple studies showing consistent results. The Subcommittee noted that due to the safety concerns, the European Medicines Agency (EMA) restricts the use of dexrazoxane injection to adult patients with advanced or metastatic breast cancer who have already received high cumulative dosages of the anthracyclines doxorubicin (300 mg/m^2) or epirubicin (540 mg/m^2) and that the treatment is contraindicated in children aged under 16 years. However, members noted that some paediatric treatment protocols currently require the use of dexrazoxane as a cardioprotective agent and that in the New Zealand setting this frequently needs to be funded by DHB hospitals because it is considered a supportive treatment.

6.6. The Subcommittee noted that dexrazoxane is registered in the United States for use in conjunction with doxorubicin, but unlike in the United Kingdom, it is not specifically contraindicated in children. The Subcommittee noted that most of the paediatric treatment protocols are from North America and the safety of dexrazoxane is generally accepted there.

6.7. The Subcommittee noted that there was a clinical need for an agent like dexrazoxane. The cardiotoxicity as a result of anthracycline therapy is clinically significant with long-term consequences especially in children. Children are exposed to longer periods of treatment with anthracyclines at a higher dose and their hearts are more sensitive to the effects of anthracyclines. The

Subcommittee considered that clinical experience indicates that there are higher mortality rates from cardiac causes when compared with second primary cancer causes in this paediatric group, with some affected children requiring cardiac transplants.

6.8. Members considered that no agent currently listed on the Schedule had a similar therapeutic effect and that lowering the dose of the anthracycline was the only alternative, which is possible in adults but not children as per current treatment protocols. The Subcommittee considered that dexrazoxane decreased cardiotoxicity by at least 50% and would allow access to better treatment regimens and protocols. The Subcommittee noted that access to dexrazoxane was needed to allow paediatric patients to participate in international clinical trials.

6.9. The Subcommittee noted that the evidence for the use of dexrazoxane is not just in the paediatric setting but there is actually better evidence for its use in adult patients. The Subcommittee noted that high dose anthracycline therapy is used to treat young patients with sarcomas, patients with Hodgkin's lymphoma and large cell lymphomas. Anthracyclines are also used to treat breast cancer but not at high doses. The Subcommittee noted that anthracyclines are also used in the palliative setting but the use of dexrazoxane should be limited to those treated with curative intent.

6.10. The Subcommittee noted that the applicant had proposed the following access criteria:

- As part of therapy for children, adolescents and young adults registered on international clinical trials;
- Infants and children aged <5 years at high risk of cardio toxicity receiving anthracycline chemotherapy totalling >250mg/m^2;
- Older children/adolescents up to 19 years with evidence of cardio toxicity with a 10% reduction in shortening fraction (ECHO); or
- Children, adolescents and young adults whose cumulative anthracycline dose has exceeded 300mg per m^2.

6.11. The Subcommittee **recommended** that dexrazoxane be funded with high priority for children, adolescent and young adults registered in international clinical trials involving high dose anthracycline therapy or treated according to those protocols. The Subcommittee **recommended** that dexrazoxane be funded with medium priority for children, adolescents and young adults who are at risk of cardiotoxicity due to treatment with high dose anthracyclines (cumulative anthracycline dose >250mg/m^2) with curative intent.

6.12. The Subcommittee **recommended** that dexrazoxane be funded subject to the following restrictions:

- Patient is a child, adolescent or young adult registered in an international clinical trial involving high dose anthracycline therapy or being treated according to the trial protocol; or

- Patient is a child, adolescent or young adult at risk of cardiotoxicity due to treatment with high dose anthracyclines (cumulative anthracycline dose >250mg/m^2) and treatment is with curative intent.

6.13. The Subcommittee noted that it would help PHARMAC staff estimate patient numbers if dexrazoxane was funded for the patient groups it proposed..

6.14. 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; (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. Everolimus for sub-ependymal giant cell astrocytomas not amenable to neurosurgical resection

7.1. The Subcommittee considered an application from a clinician on behalf of all paediatric neurologists of New Zealand.

7.2. The Subcommittee noted that the application was for patients with sub-ependymal giant cell astrocytomas (SEGAs) who were not candidates for surgical resection, and noted that PTAC had given this group a low priority. The Subcommittee noted that PTAC had added a patient category of 6 months treatment prior to surgical resection and had given this a high priority.

7.3. The Subcommittee noted (SEGAs occur in approximately 8-27% of patients with tuberous sclerosis (TSC), being an incidence of about 1-2 patients TSC per year in New Zealand. The Subcommittee noted the natural history is that these tumours generally appear in the early to mid-teenage years but frequently stop developing once the patients are aged in their 20s.

7.4. The Subcommittee noted that the genetic disorder TSC is characterised by the failure in the regulation of mTOR. It is caused by mutations in TSC1 and TSC2 gene. Members noted that everolimus is an mTOR inhibitor, and therefore an example of a molecularly targeted therapy.

7.5. The Subcommittee agreed with PTAC's summary of the evidence.

7.6. The Subcommittee noted the EXIST 1 study (Franz et al, Lancet. 2013;381 (9861):125-32) was a randomised double blind trial of 117 patients. At a median follow-up of 9.7 months, 35% of patients on everolimus experienced a 50% reduction in tumour size versus none in the placebo group ($p<0.0001$). This was independent of mutation status.

7.7. The Subcommittee noted further evidence, being an open label phase II by Krueger et al (N Engl J Med. 2010;363(19):1801-11) of 28 patients. In this study there was no deterioration on everolimus. Longer term data on this study are available in poster form (Krueger et al 2011, presented at 2011 Summit on Drug Discovery in TSC and Related Disorders, Washington DC) which reported median duration of exposure of 34 months (range 5-47 months). Reduction in volume appeared to continue with time, with 50% of the 24 participants measured at 24 months reportedly achieving a ≥50% volume reduction from baseline and 79% achieving a ≥30% reduction.

7.8. The Subcommittee considered the strength of the evidence to be moderate to high given the rarity of the condition and complexity of the endpoints.

7.9. The Subcommittee noted the side effect profile of everolimus is consistent with its profile when used in adults. Secondary amenorrhea is an issue for young women but members noted that this could be adequately managed.

7.10. Members noted that cost effectiveness modelling was difficult given the low level of evidence, but considered that it would be appropriate to assume that in patients who have been stabilised on everolimus, tumours would likely stop growing in the patients' 20s. The Subcommittee recommended that PHARMAC staff model treatment duration of 10-12 years for patients who were not amenable for neurosurgery. The Subcommittee noted it was theoretically possible for tumours to remain problematic into adulthood. The committee noted there is currently no evidence on whether it would be possible to stop everolimus treatment when patients are aged in the 20s when the disease is likely to have burnt-out.

7.11. For inoperable tumours, the Subcommittee was uncertain how many shunts these patients would receive. For operable tumours, members considered that patients are likely to receive on average 3 to 4 surgeries with up to 6 to 7 surgeries in some patients.,

7.12. The Subcommittee noted there was no evidence to suggest a different presentation of the disease in Maori or Pacific people.

7.13. The Subcommittee noted sirolimus is used off label for this indication, although the optimal dose has not been established and the suitability of sirolimus as an alternative treatment lacked evidence.

7.14. The Subcommittee disagreed with PTAC's recommendation that everolimus be funded for only short-term (6 months) treatment prior to neurosurgery in patients with SEGAs. The Subcommittee considered that complete resection is very rare and it would be difficult to stop treatment after 6 months in this patient group. The Subcommittee considered that the evidence suggests that everolimus could be used to avoid surgery altogether.

7.15. .The Subcommittee considered that everolimus should be made available to all patients with SEGAs requiring treatment and considered it was likely that some clinicians would consider the morbidity associated with neurosurgery to be unjustifiable given the availability of a drug like everolimus. The Subcommittee considered that if everolimus is funded, the special authority needs to cover the appropriate prescriber, the requirement for treatment, reassessment for continuation and duration of therapy via reapplication such as annual review or by age.

7.16. The Subcommittee **deferred** making a recommendation pending further advice from paediatric neurosurgeons, paediatric neurologists and the lead author of the Franz et al and Krueger et al studies. The Subcommittee considered that it would be helpful if paediatric neurosurgeons could clarify how everolimus would be used prior to surgery for potential debulking of a tumour. The Subcommittee considered that further advice should be sought from paediatric neurologists and the study lead authors about the appropriate length of treatment with everolimus, whether the use of everolimus would replace neurosurgery and if pre-operative use of everolimus would be curative for some patients. The Subcommittee considered that it would review this application again once advice had been obtained.