Cancer Treatments Subcommittee of PTAC
Meeting held 20 March 2015

(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 contains 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 5 & 6 November 2015.

Record of the Cancer Treatments Subcommittee of the Pharmacology and Therapeutics Committee (PTAC) meeting held at PHARMAC on 20 March 2015

1 Matters Arising and Correspondence

Pertuzumab

1.1 The Subcommittee reviewed two pieces of correspondence related to pertuzumab for HER2-positive metastatic breast cancer from Roche Products NZ limited, providing the final overall survival analysis from the Phase 3 (Cleopatra) study, and the New Zealand Breast Cancer Special Interest Group which attached the publication of the final Cleopatra data (Swain S et al; Pertuzumab, Trastuzumab, and Docetaxel in HER2-Positive Metastatic Breast Cancer (CLEOPATRA study): N Eng J Med 2015; 372:724-734).

1.2 The Subcommittee noted that the correspondence from Roche had been reviewed by PTAC at its February 2015 meeting and that at that time PTAC considered that the information provided by Roche did not change its previous view and the Committee reiterated its previous recommendation that pertuzumab should be funded with low priority.

1.3 The Subcommittee noted that the newly published evidence demonstrated that the addition of pertuzumab to trastuzumab and docetaxel improved progression-free survival by 6.3 months and overall survival by 15.7 months in women with HER2-positive metastatic breast cancer. Members considered that this was an impressive result in this setting.

1.4 The Subcommittee noted an updated cost utility analysis undertaken by PHARMAC staff using this newly published data which indicated that despite the extended overall survival benefit the cost effectiveness remained relatively poor because of the high cost of pertuzumab. The Subcommittee reiterated its previous recommendation that pertuzumab should be funded with low priority, however, members noted that the priority would improve if the price of pertuzumab decreased.

Bortezomib Tender and Special Authority

1.5 The Subcommittee noted that PHARMAC had included bortezomib in the 2014/15 Invitation to Tender. Members considered that they had no strong opposition to a sole supply being awarded for bortezomib but noted that continuity of supply was very important to this product.

1.6 The Subcommittee considered that in the event of a brand switch to a generic product being implemented in this market it would be important to provide prescribers with PK/PD data for the generic product to provide reassurance of its bioequivalence with Velcade.

1.7 The Subcommittee noted that Velcade was currently supplied in a 3.5 mg and 1 mg vial and was approved for administered via intravenous (IV) or subcutaneous routes. [redacted] Members considered it was essential that any generic could also be administered via IV or subcutaneous routes noting there was trend towards more patients receiving subcutaneous treatment. Members considered it was not necessary to also have both the 1mg and 3.5 mg vial strengths funded subject to PHARMAC confirming this was acceptable with an Oncology Pharmacist.

1.8 [redacted]

1.9 The Subcommittee noted that it had previously reviewed the Special Authority criteria for bortezomib at its March and October 2014 meetings where it had requested further information from PHARMAC staff.

1.10 The Subcommittee noted that PHARMAC receives a large number of Special Authority waiver requests for bortezomib. Members noted that in most cases applicants are seeking an extension to their patients Special Authority approval period because treatment has been delayed and they are unable to complete their planned treatment within the current Special Authority Initial approval period of 15 months.

1.11 The Subcommittee noted that over the last 2 years the number of patients treated and expenditure on bortezomib has been significantly higher than originally forecast and is still growing. Members considered that this was likely due to the change in standard treatment regimens; treatment naïve multiple myeloma patients eligible for transplant would undergo 4 cycles of bortezomib, followed by a stem cell transplant, followed by further 5 consolidation cycles of bortezomib (up to the maximum of 9 treatment cycles permitted in the current Special Authority). Members noted that this regimen was not standard of care at the time that the current Special Authority criteria were implemented. Members considered that the uptake and usage of bortezomib had reached maturity and therefore considered that growth was likely to plateau and considered that the initial approval period for bortezomib could be increased from 15 to 24 months without any financial risk.

1.12 The Subcommittee noted that the average total patient dose (lifetime) for bortezomib was currently 61 mg, however, members noted that the range around this average is very large (min 0.7 mg to max 268 mg). Members considered it would be difficult to implement a 'maximum cumulative dose' restriction without significant financial risk. Members considered that such a restriction would inadvertently increase the use of bortezomib if prescribers viewed it as an entitlement to funding for the maximum dose as they currently appear to do with the maximum number of cycles funding restriction.

1.13 The Subcommittee **recommended** that the initial approval period for bortezomib be increased from 15 to 24 months but that the rest of the Special Authority criteria remain unchanged at this time.

Gemtuzumab ozogamicin

1.14 The Subcommittee noted a new UK Medical Research Council (UK MRC) co-operative group trial, AML-19, for younger adults with favourable and intermediate-risk acute myeloid leukaemia (AML) that was to commence enrolment in New Zealand shortly. Members noted that participating in the series of prior AML studies over time had significantly increased cure rates in New Zealand from 10% to around 50% and continued participation in such trials was the standard of care approach and would likely lead to further health gains.

1.15 The Subcommittee noted that whilst several arms of the AML-19 included new investigational agents, provided free of charge by various pharmaceutical companies, one arm required treatment with gemtuzumab ozogamicin (Mylotarg, GO) which was not provided as it was considered a standard of care treatment overseas.

1.16 The Subcommittee considered that is was very important that New Zealand patients and centres should be able to participate in AML-19. Members noted that for haematologists participating in this study this would be a higher priority than some of the outstanding new funding applications. The Subcommittee **recommended** that gemtuzumab ozogamicin should be considered for listing on the Pharmaceutical Schedule.

1.17 The Subcommittee noted that it was very supportive of New Zealand centres and patients participating in clinical trials and **recommended** that PHARMAC develop a mechanism for funding treatments for non-industry clinical trials. Members considered that setting up a contestable fund for clinical trial treatment funding may be a reasonable approach.

2 Trastuzumab Subcutaneous

Application

2.1 The Subcommittee considered an application from Roche Products NZ Ltd for the funding of subcutaneous trastuzumab (Herceptin SC) for the treatment of HER2 positive early, locally advanced or metastatic breast cancer. The Subcommittee also considered a supporting application from The Breast Cancer Special Interest Group.

Recommendation

2.2 The Subcommittee **recommended** that subcutaneous trastuzumab should be funded for the treatment of HER2 positive early, locally advanced or metastatic breast cancer with low priority. The Subcommittee noted that its low priority recommendation was driven by the current pricing offered for subcutaneous

trastuzumab and that its priority rating would increase if the price was more competitive compared with future biosimilar IV trastuzumab.

2.3 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; (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; (vii) The direct cost to health service users; and (viii) The Government's priorities for health funding, as set out in any objectives notified by the Crown to PHARMAC, or in PHARMAC's Funding Agreement, or elsewhere.*

Discussion

2.4 The Subcommittee noted that the application from Roche and supporting application from The Breast Cancer Special Interest Group were both reviewed by PTAC at its November 2014 meeting where it recommended that the application be declined.

2.5 The Subcommittee noted that this application was for an alternative subcutaneous (SC) formulation of trastuzumab that was administered at a fixed dose of 600mg/5mL over approximately 5 minutes every three weeks compared with the currently funded intravenous (IV) formulation administered at a dose of 8 mg/kg for the first dose over 90 minutes, with subsequent maintenance doses of 6 mg/kg over 30 minutes every 3 weeks.

2.6 The Subcommittee considered that there were four aspects to take into account when considering this application; the evidence, the practicalities of administration to patients, the current cost of IV trastuzumab and the future cost of IV trastuzumab.

2.7 The Subcommittee considered evidence for SC trastuzumab from the HannaH study that was an open label randomised non-inferiority Phase III trial of neoadjuvant trastuzumab in women with HER2-positive stage I to IIIC breast cancer (Ismael G et al Lancet Oncol 2012; 13(9): 869-78). Members noted that 596 patients were randomised 1:1 to receive 8 cycles of neoadjuvant chemotherapy administered concurrently with trastuzumab every 3 weeks either IV (n=299) or SC (n=297), after surgery, patients continued to receive trastuzumab as assigned (IV or subcutaneously) to complete 1 year (18 cycles) of treatment. Members noted that the co-primary endpoints of the trial were C_{trough} recorded before surgery (predose cycle 8) and pathological complete response (pCR) after 8th cycle of chemotherapy and surgery.

2.8 The Subcommittee noted that results from the Hannah study indicated that SC trastuzumab was non-inferior to IV trastuzumab in the co-primary endpoints. Members considered that whilst neoadjuvant trastuzumab treatment was not the standard of care in New Zealand at present it was likely that you would expect similar results in other settings, e.g. adjuvant or metastatic disease. However,

members noted evidence from an early pharmacokinetic study of IV trastuzumab demonstrated that the number of metastatic sites, plasma level of extracellular domain of the HER2 receptor, and patient weight were significant predictors of trastuzumab exposure (Bruno et al Cancer Chemotherapy and Pharmacology October 2005; 56(4): 361-369). Members considered that it was possible that the efficacy of fixed dose SC trastuzumab in some metastatic patients could be different to weight-based IV dosing, especially for patients with a large number of metastatic sites and/or high body weight.

2.9 The Subcommittee also considered evidence from the PrefHer study, an international open label randomised cross over patient preference study in women with HER2-positive early breast cancer (Pivot et al Lancet Oncol 2013; 14: 962–70) which demonstrated that women preferred the SC formulation noting that the two main reasons for preference stated by patients were either it saved time or caused less pain and discomfort. Members noted that observational time and motion (TAM) sub-studies were undertaken within the PrefHer study to quantify health care professional (HCP) time associated with preparation and delivery of IV and SC trastuzumab and the duration that patients sat in infusion chairs. Members noted that an analysis in UK centres published by Burcombe et al (Adv Breast Can Res. 2013;2:133-40) reported a mean health care professional time saving of 68 minutes and mean infusion chair time saving of 55 minutes for SC administration over IV administration per treatment cycle.

2.10 The Subcommittee also noted results from an unpublished TAM study in two New Zealand centres participating in SafeHer, a non-randomized, open-label study evaluating the safety and tolerability of SC and IV trastuzumab as adjuvant therapy in patients with early HER2-positive breast cancer showing that the use of SC trastuzumab reduced mean chair time by 37 minutes.

2.11 The Subcommittee considered that the evidence demonstrated that SC trastuzumab delivered similar efficacy and would likely save hospital resources compared with IV trastuzumab. Members considered that whilst hospital resource savings would be unlikely to deliver direct cost savings in the short term, in practice it would deliver staffing and other resource efficiencies enabling more patients to be treated in DHB hospitals which would likely be associated with some health gain. Members considered it was wrong to assume that because DHBs were currently achieving their cancer health targets capacity in DHBs was not constrained or that increasing efficiency would not be of benefit to service delivery. Members noted that the ageing population would continue to put more strain on service capacity into the future and that staffing and other resource increases cannot continue to increase to meet that demand.

2.12 The Subcommittee considered that whilst it may be possible to administer SC trastuzumab in a primary care facility, or even at home, for most DHBs such services would be unlikely to implemented in the near term.. Members considered that trastuzumab treatment required oncologist supervision for all doses and availability of cardiac resuscitation support for at least the first dose where allergic reactions, if they occur at all, are most commonly observed. Members considered that services would need to be reconfigured to allow trastuzumab to be administered in the community and it was more likely that such a service would be a satellite oncology clinic rather than a GP or at home setting.

2.13 The Subcommittee considered that in practice SC trastuzumab would be most suitable for patients receiving monotherapy trastuzumab treatment. Members considered that there would be little time benefit to patients or hospital resources where patients were receiving trastuzumab in combination with other chemotherapy treatments.

2.14 The Subcommittee considered that currently in the adjuvant setting approximately two thirds of trastuzumab cycles would be given as monotherapy treatment (the last 13-14 cycles of an 18 cycle treatment regimen), whereas in the metastatic setting members considered that approximately half of trastuzumab cycles would be given as monotherapy. Overall Members considered that 50-70% of current IV trastuzumab use could be replaced by SC trastuzumab.

2.15 The Subcommittee considered that SC trastuzumab may reduce the number of patients needing a peripherally inserted central catheter (PICC) line or portacath, or limit the duration of the use of these devices and their associated complications. However, members noted that currently the use of these devices was not consistent across centres so it was difficult to estimate the national impact of any change.

2.16 The Subcommittee noted that the 600 mg fixed dose per cycle of SC trastuzumab was higher than the average dose per cycle of IV trastuzumab currently delivered in practice based on claiming data (436 mgs/per cycle for early breast cancer patients and 428 mgs/cycle for metastatic breast cancer patients). Members considered that it was unclear from the available evidence if the increased dose of SC trastuzumab would have an adverse impact on the known cardiovascular toxicity of trastuzumab treatment. Members considered that patients who weighed more than 110 KG would likely be under-dosed with SC trastuzumab formulation and therefore considered that such patients should be treated with IV trastuzumab.

2.17 The Subcommittee considered that whilst SC trastuzumab did offer some clinical and resource advantages over IV trastuzumab the introduction of SC trastuzumab would make it very difficult to generate savings from competition from the introduction of biosimilar IV trastuzumab in the future. Members considered that the potential cost savings achievable from biosimilar IV trastuzumab competition would outweigh the resource and clinical advantages for SC trastuzumab at the current pricing offered. Members noted that the price of SC in the UK (as listed in the British National Formulary) was lower than the pricing offered by the supplier in its application.

3 Sunitinib and Temozolomide for NETs

Application

3.1 The Subcommittee reviewed an application from Pfizer for the funding of sunitinib (Sutent) for the treatment of well differentiated, unresectable pancreatic neuroendocrine tumour (pancreatic NET) in patients who are symptomatic (despite somatostatin analogues) or have documented disease progression. The

Subcommittee also reviewed an application from PHARMAC staff for the funding of temozolomide, in combination with capecitabine, and other treatments for unresectable NET.

Recommendation

3.2 The Subcommittee **recommended** that the application for sunitinib be declined. The Subcommittee further **recommended** that temozolomide be funded for patients with unresectable, well-differentiated (low grade) NET with medium priority.

3.3 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 and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule*

Discussion

3.4 The Subcommittee noted that the application from Pfizer for sunitinib and the application from PHARMAC staff for the use of temozolomide and other treatments, including evidence received with NPPA funding applications, was considered by PTAC at its February 2015 meeting. Members noted that PTAC deferred making a recommendation pending further advice from CaTSoP.

3.5 The Subcommittee noted that neuroendocrine tumours (NETs) are a heterogeneous group of tumours that differ in biologic behaviour, histologic appearance, and response to treatment. Members noted that some NETs are non-functioning (not associated with a hormonal secretions and syndrome) whereas functioning NETs are characterised by the type of hormone secreted e.g. insulinoma, gastrinoma, thymoma, glucagonoma or vasoactive intestinal peptidoma (VIPoma), which cause a variety of clinical syndromes depending on the type of secretion. Members noted that NETs are classified according to their histologic features which separate more indolent (low grade), well differentiated tumours and more aggressive (high grade) poorly differentiated tumours that are often managed similarly to small cell lung cancer with platinum based chemotherapy combined with radiation therapy.

3.6 The Subcommittee noted that Peptide receptor radionuclide therapy (PRRT) was a promising, and relatively cheap, new treatment for NETs, however, members noted that it required specialised services to attach radionuclides to octreotide which were not currently available in New Zealand. Members noted that some patients were travelling to Australia to receive this treatment.

3.7 The Subcommittee noted that PHARMAC had received a large number of NPPA applications for the funding of various treatments, primarily streptozocin and more recently temozolomide, for patients with various NETs (including pancreatic

NETs) some of which had been approved. Members considered that historically streptozocin was the standard of care treatment for unresectable NETs, but noted that this treatment was neither approved by Medsafe nor listed on the Hospital Medicine List. Members considered that streptozocin probably should have been included on the HML when it was implemented but noted that it was a high cost medicine and because it had worldwide orphan drug status considered that the cost was unlikely to decrease in the future.

3.8 The Subcommittee reviewed evidence for sunitinib from a randomised, double-blind, placebo-controlled Phase III study comparing the efficacy and safety of sunitinib administered daily at a dose of 37.5 mg (n=86) with placebo (n=85) in patients with histologically or cytologically proven diagnosis of well-differentiated local, locally advanced or metastatic progressive pancreatic islet cell tumour (pancreatic NET) (study A6181111, Raymond E et al. N Engl J Med. 2011;364(6):501-513). Members noted that treatment was continued until disease progression, unacceptable toxicity or death and that at the time of disease progression, patients were un-blinded and if randomised to placebo offered open-label sunitinib.

3.9 The Subcommittee noted that the primary endpoint was progression free survival (PFS) and the study was powered for a 50% improvement of sunitinib over placebo. Members noted that the study was stopped early by the Data and Safety Monitoring Committee (DSMC) after less than half of the planned PFS events had been observed and all remaining placebo patients were offered sunitinib. Members noted that the reasons given for stopping the study early due were more serious adverse events and deaths in the placebo group and a PFS difference at that time that favoured sunitinib (median PFS 11.4 months for sunitinib vs. 5.5 months for placebo (hazard ratio, 0.42; 95% confidence interval [CI], 0.26 to 0.66; P<0.001). Members noted that there was no overall difference in quality of life between the treatment groups despite the PFS gains and there were no new safety signals for sunitinib compared with data in other settings (renal cell carcinoma and gastrointestinal stromal tumour) despite the different dosing schedule.

3.10 The Subcommittee noted that the study design, which allowed placebo patients to cross over to sunitinib on disease progression, confounded overall survival data and the early stopping of the study confounded these data further. Members noted that the supplier had undertaken 4 different statistical methods in an attempt to adjust for the cross-over effect on survival data. Members considered that none of these methods were regarded as equivalent to observed survival data from an unconfounded study. Members agreed with PTACs view that because of the study being stopped early and the confounding of survival data, the strength and quality of the evidence provided for sunitinib was moderate.

3.11 The Subcommittee reviewed evidence from a number of prospective and retrospective studies of streptozocin, dacarbazine or temozolomide, alone or in combinations with other treatments, in metastatic NETs.

3.12 The Subcommittee noted that one randomized trial in advanced pancreatic NET cancer (Islet cell carcinoma) the combination of streptozocin plus doxorubicin

reported a 69% response rate with median survival of 2.2 years (Moertel et al. N Engl J Med 1992; 326:519). Members further noted a retrospective analysis of 84 patients with either locally advanced or metastatic pancreatic NETs treated with streptozocin, 5-FU, and doxorubicin that reported a 39% response rate and a median survival duration of 37 months (Kouvaraki et al. J Clin Oncol 2004;22:4762). Members considered that whilst streptozocin-based regimens were clearly active in patients with advanced pancreatic NET, its widespread use had likely been limited by its high cost and, its relatively cumbersome administration schedule and toxicity concerns.

3.13 The Subcommittee noted an Eastern Cooperative Oncology Group (ECOG) phase II trial of dacarbazine in 42 patients with advanced pancreatic islet cell carcinoma that reported a 33% objective response rate (Ramanathan et al. Ann Oncol 2001;12:1139). Members noted that temozolomide was a less toxic orally active analogue of dacarbazine.

3.14 The Subcommittee noted a retrospective study of 30 patients treated with capecitabine (750 mg/m2 twice daily on days 1 to 14) plus temozolomide (200 mg/m2 daily on days 10 to 14) that reported a response rate of 70% (Strosberg et al. Cancer 2011;117:268) and a preliminary report from a small phase II trial of the same regimen in patients with advanced pancreatic NET presented at the 2014 American Society of Clinical Oncology Gastrointestinal Cancers Symposium that reported an objective partial response of 36% with a median progression-free survival of >20 months (Fine, et al. J Clin Oncol 32, 2014 (suppl 3; abstr 179). Members noted results from a number of other studies combining temozolomide with other agents (thalidomide, everolimus and bevacizumab).

3.15 The Subcommittee noted an ongoing randomised Phase III ECOG study evaluating temozolomide plus capecitabine (CAPTEM) versus temozolomide alone. Members considered that CAPTEM was a well thought out oral regimen that would likely be efficacious in all low grade NETs with expected response rates of 60-70% based on previous evidence with median PFS in the region of 14-18 months. Members also noted that the regimen would likely be very well tolerated and was relatively low cost.

3.16 The Subcommittee noted that there was a correlation between deficient expression of methylguanine DNA methyltransferase (MGMT) in tumours and temozolomide responsiveness, members noted that the prevalence of MGMT deficiency was high in pancreatic NETs but noted that this data was preliminary and needed further validation in clinical trials before testing for MGMT expression levels could be routinely recommended.

3.17 The Subcommittee considered that patients with unresectable, well-differentiated (low grade) NETs would likely need multiple lines of treatment. Members considered that at least one line treatment should be funded on the Pharmaceutical Schedule and considered that taking into account expected efficacy, ease of administration, tolerability and cost temozolomide, in combination with capecitabine, was the preferred, and likely the most cost-effective, treatment option available.

3.18 The Subcommittee considered that if further lines of treatment were to be funded their preference, taking into account including ease of use, efficacy and cost would be, temozolomide in combination with capecitabine as first line treatment, followed by streptozocin second line, followed by sunitinib third line.

4 Zoledronic Acid for Breast Cancer

Application

4.1 The Subcommittee reviewed an application from the New Zealand Breast Cancer Special Interest Group (NZBCSIG) for the funding of zoledronic acid (Zometa) for adjuvant use in postmenopausal women with early breast cancer to reduce the risk of recurrence with bone metastases and to improve survival.

Recommendation

4.2 The Subcommittee **recommended** that zoledronic acid should be funded for adjuvant use in postmenopausal women with early breast cancer, with low priority. Members considered that if zoledronic acid was to be funded it should be dosed at 4 mg every 6 months for a maximum of 3 years.

4.3 The Subcommittee further **recommended** that it reconsider the Coleman 2013 meta-analysis once it has been fully published.

4.4 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 zoledronic acids and related things; (iv) The clinical benefits and risks of pharmaceuticals and (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publically funded health and disability support services.*

Discussion

4.5 The Subcommittee noted that this application was for the funding of adjuvant zoledronic acid, given at 6 monthly intervals for 5 years, in postmenopausal women with early breast cancer to reduce the risk of breast cancer recurrence with bone metastases and to improve breast cancer survival. Members noted that the application had been reviewed by PTAC at its February 2015 meeting where it recommended that the application be declined and referred to CaTSoP for review.

4.6 The Subcommittee noted that zoledronic acid is a bisphosphonate treatment administered by infusion. Members noted that zoledronic acid 0.8 mg per ml, 5 ml (Zometa) is currently funded subject to Special Authority criteria for hypercalcaemia of malignancy, and treatment of pain and prevention of skeletal-related events in patients with bone metastases. Members noted several other bisphosphonates were also funded on the Pharmaceutical Schedule including oral risedronate, etidronate and intravenous pamidronate that are funded without

restriction and oral alendronate and zoledronic acid (5 mg in 100 mL, Aclasta) that are funded subject to Special Authority criteria for treatment of osteoporosis.

4.7 The Subcommittee reviewed evidence from several studies and meta-analyses. Members considered that the key evidence for the proposed funding comprised two open label randomised controlled trials of adjuvant zoledronic acid treatment, and Austrian Breast and Colorectal Cancer Study Group trial (ABCSG-12, Gnant et al. Lancet Oncol. 2011;12(7):631-41; Gnant et al. Annals of Oncology 2015;26:313–20) and AZURE (Coleman et al. N Engl J Med. 2011;365:1396-405; Coleman et al. Lancet Oncol. 2014;15:997-1006). The Subcommittee noted that ABCSG-12 study was a 4 arm study comparing the efficacy and safety of anastrozole (1 mg per day) compared with tamoxifen (20 mg per day) both with or without zoledronic acid (4 mg every 6 months) for 3 years. Members noted that the study enrolled 1803 premenopausal women with stage I/II oestrogen-receptor-positive and/or progesterone-receptor-positive breast cancer with <10 positive lymph nodes, with all patients receiving ovarian suppression with goserelin (3.6 mg every 28 days). Members noted that the primary endpoint of disease-free survival (defined as time from randomisation to the first occurrence of any of the following: a local or regional recurrence, contralateral breast cancer, distant metastasis, second primary carcinoma, and death from any cause) with secondary endpoints of recurrence-free survival, overall survival and bone mineral density and safety. Members noted that bone metastasis disease free survival was an exploratory endpoint.

4.8 The Subcommittee noted that in the ABCSG-12 study at 94.4 months (7 years 10 months) median follow-up, zoledronic acid reduced risk of disease-free survival (DFS) events [hazard ratio (HR) = 0.77; 95% confidence interval (CI) 0.60-0.99; P = 0.042], but did not statistically significantly impact overall survival (OS) (HR = 0.66; 95% CI 0.43-1.02; P = 0.064). Members noted that the absolute risk reductions with zoledronic acid were 3.4% for DFS and 2.2% for OS. Members noted that there were no reports of were no reports of osteonecrosis of the jaw.

4.9 The Subcommittee noted that the AZURE study enrolled 3360 pre and postmenopausal women with stage II or III breast cancer who were randomised 1:1 to receive standard adjuvant systemic chemotherapy treatment alone (control group) or with 4 mg intravenous zoledronic acid every 3-4 weeks for six doses, then every 3 months for eight doses, followed by every 6 months for five doses, for a total of 5 years of treatment. Members noted that the primary endpoint was DFS with secondary endpoints including invasive DFS (IDFS), OS, time to bone metastases and time to distant recurrence. The Subcommittee noted that there was no significant difference in the number of DFS events (HR 0.94, 95% CI 0.82–1.06; p=0.30), IDFS (HR 0.93, 95% CI 0.82–1.05; p=0.22), overall survival (0.93, 95% CI 0.81–1.08; p=0.37), or distant recurrences (0.93, 0.81–1.07; p=0.29) between treatment groups. However, zoledronic acid reduced the development of bone metastases, both as a first event (HR 0.78, 95% CI 0.63–0.96; p=0.020) and at any time during follow-up (0.81, 0.68–0·97; p=0.022) and improved IDFS in those who were over 5 years since menopause at trial entry (n=1041; HR 0.77, 95% CI 0.63–0.96). Members also noted that 33 cases of suspected osteonecrosis of the jaw were reported, with 26 confirmed on central review, all in the zoledronic acid group (1.7%, 95% CI 1.0–2.4). Members considered that the high incidence of osteonecrosis of the jaw seen in this study

was likely due to the dose dense dosing of zoledronic acid compared with a more standard 6 monthly dosing regimen as used in ABCSG-12.

4.10 The Subcommittee noted the contrasting results of these 2 studies but noted that whilst the end points of both studies were similar, the dosing schedules of zoledronic acid used and populations enrolled in each study were different. Members noted that neither study used the dosing schedule being requested for funding by the applicants of 4mg of zoledronic acid given at 6 monthly intervals for 5 years. Members noted that these were the only two randomised trials reported to date that were specifically designed and powered to explore recurrence as the primary endpoint, noting that the majority of bisphosphonate studies in breast cancer were primarily designed on bone mineral density or skeletal related events endpoints.

4.11 The Subcommittee also noted an abstract of an unpublished meta-analysis of data from 17,751 women with early breast cancer from 41 randomised trials comparing bisphosphonates to no bisphosphonates presented by Coleman et al at the San Antonio Breast Cancer Symposium (SABCS) in December 2013. The Subcommittee noted that the abstract reported that treatment with bisphosphonates reduced breast cancer recurrence by 1.7% at 10 years but members considered that there was insufficient detail provided in the abstract to draw any definitive conclusions about this result.

4.12 The Subcommittee noted a Cochrane Collaboration Review of bisphosphonates and other bone agents for breast cancer (Wong et al Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD003474. DOI: 10.1002/14651858.CD003474.pub3.2012). Members noted that the review assessed the effect of bisphosphonates on skeletal-related events, bone pain, quality of life, recurrence and survival in women with breast cancer with bone metastases, advanced breast cancer without bone metastases and early breast cancer. Members noted that the authors concluded that in patients with early breast cancer (comprising data from 7847 patients with early breast cancer from 7 studies (3 zoledronic acid, 3 clodronate and 1 pamidronate) including ABCSG-12 and AZURE) there is no evidence to support use of bisphosphonates to reduce the incidence of bone metastases and there is insufficient evidence to make a conclusion about the role of adjuvant bisphosphonates in reducing visceral metastases, locoregional recurrence and total recurrence, or improving survival.

4.13 The Subcommittee also reviewed evidence from an open-label phase 3 RCT in 1065 postmenopausal women with early breast cancer receiving adjuvant letrozole (2.5 mg/day for 5 years), in which patients were randomly assigned to immediate zoledronic acid 4 mg every 6 months for 5 years, or delayed zoledronic acid (initiated for fracture or on-study bone mineral density [BMD] decrease) ZO-FAST trial (Coleman et al. Ann Onc 2013;24:398-405). Members noted that the primary endpoint of this study was change in lumbar spine BMD at 12 months but DFS and OS outcomes were assessed as secondary endpoints. Members noted that at 60 months the mean change in lumbar spine BMD was +4.3% with immediate zoledronic acid vs. -5.4% with delayed intervention

(p<0.0001). Members further noted that immediate zoledronic acid reduced the risk of DFS events by 34% (HR =0.66, 95% CI 0.44–0.97; P = 0.0375) with fewer local (0.9% versus 2.3%) and distant (5.5% versus 7.7%) recurrences compared with delayed zoledronic acid whereas OS was not substantially different between groups (HR = 0.69; 95% CI = 0.42–1.14; P = 0.1463).

4.14 The Subcommittee considered that there were real challenges determining with any certainty the benefits of zoledronic acid on breast cancer recurrence and survival from the available evidence noting the variability in results, populations enrolled, dosing schedules and bisphosphonate used in the various studies. Members considered it was likely that there was a bisphosphonate class effect rather than a specific effect of zoledronic acid itself. Members noted that there was no evidence to support zoledronic acid being more effective than other bisphosphonates in this setting, notably IV pamidronate or oral clodranate, however, members noted that there was currently no use of other bisphosphonates for the proposed treatment in practice despite several being funded without restriction. Members considered that oral bisphosphonates would likely be cheaper than zoledronic acid or pamidronate when taking into account DHB hospital administration costs and members also noted that prior to starting zoledronic acid patients would need a dental check which may have significant resource implications for DHBs. Members considered that given the large number of patients with early breast cancer it would be more practical to fund an oral bisphosphonate treatment. Members considered that ideally further clinical trials should be conducted comparing the various bisphosphonates, however, members noted that such studies were unlikely to be conducted.

4.15 Members considered that a cost utility analysis comparing zoledronic acid with no treatment and other bisphosphonates should be performed. Members considered it may be reasonable to limit funding to postmenopausal early breast cancer patients with a higher risk of recurrence.

5 Obinutuzumab for CLL

Application

5.1 The Subcommittee considered an application from Roche Products NZ limited for the funding of obinutuzumab (Gazyva) for the first-line treatment of patients with chronic lymphocytic leukaemia (CLL) with comorbidities.

Recommendation

5.2 The Subcommittee **recommended** that obinutuzumab should be funded for patients with chronic lymphocytic leukaemia who have comorbidities preventing treatment with fludarabine, cyclophosphamide and rituximab. The Subcommittee gave this recommendation a medium priority

5.3 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 zoledronic acids and related things; (iv) The clinical benefits and risks of*

pharmaceuticals and (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publically funded health and disability support services.

Discussion

5.4 The Subcommittee noted that this application was reviewed by PTAC at its February 2015 meeting where it recommended it be funded with medium priority. Members also noted that PTAC recommended the application be reviewed by CaTSoP for further advice on: (i) what proportion of patients are currently receiving chlorambucil monotherapy, (ii) how the overall CLL treatment paradigm would be affected by the funding of obinutuzumab, and (iii) appropriate Special Authority funding restriction criteria for obinutuzumab.

5.5 The Subcommittee noted that current standard of care treatment for patients with CLL requiring treatment was rituximab in combination with fludarabine, and cyclophosphamide (FCR). However, members noted that for older patients and/or those with co-morbidities dose modified FCR or chlorambucil monotherapy is used.

5.6 The Subcommittee noted primary evidence for the proposed funding comprised an open-label, multicentre, randomised controlled, phase III study, CLL-11 (Goede V et al. N Engl J Med 2014; 370: 1101-10). Members noted that the study enrolled 781 patients with previously untreated CLL and a score higher than 6 on the Cumulative Illness Rating Scale (CIRS) or an estimated creatinine clearance of 30 to 69 ml per minute with patients randomised on a 1:2:2 basis to receive chlorambucil (Clb, n=118) obinutuzumab plus chlorambucil (G-Clb, n=331), or rituximab plus chlorambucil (R-Clb, n=331) for a total of six 28-day cycles. Members noted that chlorambucil was administered orally at a dose of 0.5 mg per kg on days 1 and 15 of each cycle, obinutuzumab was administered IV at dose of 1000 mg on days 1, 8, and 15 of cycle 1 and on day 1 of cycles 2-6 (after amendment of the study protocol, the first infusion of obinutuzumab was administered over a period of 2 days) and rituximab administered IV at a dose of 375 mg/m^2 day 1 of cycle 1 and 500 mg/m^2 on day 1 of cycles 2-6.

5.7 The Subcommittee noted that the study had two stages with randomisation to the Clb arm stopped once 118 eligible patients were allocated and patients in the Clb arm were allowed to cross over to the G-Clb arm for progressive disease or within 6 months after the end of treatment. Members noted that the primary end point of the study was investigator-assessed progression-free survival.

5.8 The Subcommittee noted that patients had a median age of 73 years, creatinine clearance of 62 ml per minute, and CIRS score of 8 at baseline with 82% having more than three co-existing conditions.

5.9 The Subcommittee noted that treatment with either obinutuzumab–chlorambucil or rituximab–chlorambucil, significantly improved median progression-free survival compared with chlorambucil alone (26.7 months G-Clb vs. 11.1 months Clb; hazard ratio for progression or death, 0.18; 95% confidence interval [CI], 0.13 to 0.24; P<0.001; and 16.3 months R-Clb vs. 11.1 months Clb; HR, 0.44; 95% CI, 0.34 to 0.57; P<0.001). Members further noted that G-Clb significantly

prolonged progression-free survival compared with R-Clb (median progression-free survival, 26.7 vs. 15.2 months; hazard ratio, 0.39; 95% CI, 0.31 to 0.49; P<0.001) and resulted in higher rates of overall, complete, and molecular responses. Members noted that G-Clb significantly improved overall survival compared with R-Clb (rate of death 8% vs 12% HR 0.66; 95% CI, 0.41 to 1.06; P = 0.08) and Clb alone (rate of death 9% vs 20% HR 0.41; 95% CI, 0.23 to 0.74; P = 0.002), whereas, no significant survival benefit was observed for R-Clb compared with Clb (rate of death 15% vs 20%, HR 0.66; 95% CI, 0.39 to 1.11; P = 0.11).

5.10 The Subcommittee considered that overall the evidence supported that the addition of obinutuzumab to chlorambucil significantly improved CLL treatment outcomes. Members considered that the supplier's estimates for the number of patients currently with comorbidities and receiving chlorambucil were probably accurate, however, members considered that there may be a larger group of patients currently receiving dose modified FCR, due to marginal co-morbidities or toxicity, who would likely access obinutuzumab treatment if it were funded. Members considered that the size of this group of patients was difficult to accurately estimate.

5.11 The Subcommittee considered that because of the high cost of obinutuzumab it was important for the Special Authority criteria to clearly target treatment to the patients with highest health need who were currently not able to receive FCR at all. Members considered this would be difficult to do even with criteria based on the CLL-11 study entry criteria and considered that some slippage would still be very likely.

5.12 The Subcommittee also noted that studies were currently underway comparing obinutuzumab with rituximab both in combination with fludarabine, and cyclophosphamide (G-FC vs. FCR) in fit CLL patients and if results demonstrated an improvement for G-FC over FCR would likely lead to more patients accessing obinutuzumab if it were funded.

5.13 The Subcommittee noted that a large number of new treatments had recently been approved or were in late stages of development for treatment of CLL and treatment approaches and pathways for CLL were rapidly changing. Members noted in particular that ofatumumab and bendamustine may have a place either as monotherapy or in combination with obinutuzumab, and ibrutinib and idelalisib were promising new oral treatments.

6 Plerixafor for autologous stem cell transplantation

Application

6.1 The Subcommittee reviewed an application from a clinician for the inclusion of plerixafor (Mozobil) on the Hospital Medicines List (HML) for use in peripheral stem cell mobilisation.

Recommendation

6.2 The Subcommittee **recommended** that plerixafor is listed in Part II of Section H of the Pharmaceutical Schedule with high priority subject to the following restriction criteria:

Plerixafor
Restricted
Autologous stem cell transplant – haematologist
Both:
1. Patient is undergoing stem cell transplantation; and
2. Either:
   2.1 Patient is undergoing G-CSF mobilisation; and
      2.1.1 Either:
         2.1.1.1 Has a suboptimal peripheral blood CD34 count of ≤ 10 x 10^6 / L on day 5 after 4 days of G-CSF treatment; or
         2.1.1.2 Efforts to collect >1×10^6 CD34 cells/ kg have failed after one apheresis procedure; or
   2.2 Patient is undergoing chemotherapy and G-CSF mobilisation; and
      2.2.1 One of the following:
         2.2.1.1 Has rising white blood cell counts of > 5 – 10 x 10^9 / L and a suboptimal peripheral blood CD34 count of ≤ 10 x 10^6 / L;
         2.2.1.2 Efforts to collect >1×10^6 CD34 cells/ kg have failed after one apheresis procedure; or
         2.2.1.3 The peripheral blood CD34 cell counts are decreasing before the target has been received.

6.3 The Subcommittee **recommended** that PHARMAC staff update the cost-utility analysis for plerixafor with the information provided by the Subcommittee at this meeting for review by PTAC when PTAC reviews this funding application.

6.4 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.*

Discussion

6.5 The Subcommittee noted that it had reviewed this application at its meetings in September 2013, March 2014 and October 2014. The Subcommittee noted that it had previously deferred making a recommendation on the product until after it completed a cost-utility analysis (CUA) for its review. The Subcommittee noted that the product is not yet Medsafe-registered but registration is possible within the next few months.

6.6 The Subcommittee noted the results of the CUA completed by PHARMAC staff. The Subcommittee considered that almost no patients in whom there has been a failure to collect >2 x 106 CD34 cells/kg stem cells proceed to transplantation. The patient groups who potentially proceed to transplant are patients with

relapsed Hodgkin's Lymphoma (HL) and relapsed large cell lymphoma where there is a high cure rate.

6.7 The Subcommittee noted that patients who proceed to autologous stem cell transplants (ASCT) have fewer complications if adequate numbers of stem cells are harvested (>2 x 106 CD34 cells/kg) compared to sub-optimal harvest numbers. The Subcommittee noted that slow engraftments are associated with longer hospital stays. It is difficult to specifically define the difference in complication rates but the Subcommittee considered that the assumption of 8% (adequate mobilisation) versus 13% (inadequate mobilisation) is reasonable.

6.8 The Subcommittee agreed with assumptions made by PHARMAC staff for the proportion of patients with HL and non-Hodgkin's Lymphoma (NHL) treated with ASCT who would be alive after 5 and 10 years (PHARMAC staff estimated 58% and 49% of HL patients to be alive at 5 and 10 years respectively, and 52% and 33% of NHL patients to be alive at 5 and 10 years respectively). The Subcommittee considered that for patients with HL and large cell lymphoma, they would be considered cured of the disease if they have not relapsed within 5 years after the ASCT. The Subcommittee considered that in NHL, some ASCTs are done in those with low grade disease but it would not be curative as most patients would relapse. The Subcommittee considered that PHARMAC's assumptions for the survival rates of patients with HL and NHL treated with ASCT and with only chemotherapy (without ASCT) are appropriate.

6.9 The Subcommittee noted that the CUA for NHL and HL patients is sensitive to the cost of subsequent chemotherapy that relapsed patients may or may not receive. The Subcommittee noted that in patients with HL who relapse, some will have indolent disease which would respond well to multiple rounds of chemotherapy. In patients with NHL, they would normally only receive another 1 to 2 lines of chemotherapy before treatment becomes palliative.

6.10 The Subcommittee noted that in 2011, there were 127 autologous stem cell transplants performed in New Zealand. The Subcommittee considered that about 5% of patients who undergo stem cell mobilisation do not proceed to transplant, mainly because of disease progression, especially in patients with lymphoma. The Subcommittee considered that it would be appropriate to assume that currently approximately 150 patients would undergo ASCT for lymphoma and multiple myeloma a year. Published preemptive algorithms result in plerixafor use in initial stem cell mobilisation ranging from 14.4% in patients mobilised with chemo/G-CSF (Milone et al. Brit J Haematol 2014;164:113-23) to 35% in patients mobilised with G-CSF alone (Abhyankar et al. Bone Marrow Transplant 2012; 47(4):483-7). The Subcommittee noted that the funding of plerixafor would not change the number of patients undergoing mobilisation procedures but it would reduce repeat mobilisations. If it is assumed that 15-35% of patients who undergo mobilisation end up requiring plerixafor under a pre-emptive strategy, 20 to 50 patients could access plerixafor per year. Assuming plerixafor is effective in 80% of patients using plerixafor in a preemptive way means 95% patients are successful in first mobilisation attempt and on remobilisation with plerixafor the remaining few usually mobilise with failure of 1.9% only (Abhyankar et al. Bone Marrow Transplant 2012;47(4):483-7).

6.11 The Subcommittee considered that currently only a small group of patients (5-10%) fail mobilisation in New Zealand without plerixafor. In those situations, more collections and remobilisations with higher G-CSF and chemotherapy doses would be done. This however requires significant clinical effort and results in significant patient discomfort. Therefore, the availability of plerixafor would not change the number of patients undergoing ASCT significantly but it will make ASCT easier and more efficient for health services and patients.

6.12 The Subcommittee considered that it would be appropriate to list plerixafor for pre-emptive use prior to ASCT. The Subcommittee noted that the access criteria should be based on the applicant's proposed wording and guidelines provided in the Jantunen et al study (Expert Opin Biol Ther 2014;14(6):851-61). The Subcommittee noted that patients would on average require 2 doses only.

6.13 The Subcommittee considered that although plerixafor is significantly more expensive than current treatment options it improves stem cell yield, allows for successful remobilisation of patients who have previously failed standard mobilisation attempts and if used in a pre-emptive algorithm, it would reduce the rate of initial failure of stem cell collection. The Subcommittee considered that its initial draft restriction criteria was not evidence-based but was drafted as a very restrictive pre-emptive algorithm because of significant cost concerns. The Subcommittee considered that plerixafor would enable hospitals to use resources including clinician time and plasmapheresis more efficiently. It would also reduce weekend mobilisations.

6.14 The Subcommittee recommended a major change to the proposed restriction criteria recognising that this will lead to considerably greater use of plerixafor. The Subcommittee recommended that the cost-utility of this change is assessed by PHARMAC and compared with a more restrictive approach for use of plerixafor, only for failed stem cell mobilization where its use would be in about 10% of patients undergoing mobilisation. The Subcommittee considered that if the tighter restriction is put in place, criteria for failed stem cell mobilisation would then need to be defined carefully in the restriction due to the risk of slippage.

6.15 The Subcommittee noted that its recommended criteria do not take into account situations where large stem cell collections are needed for several staged transplants, for example in germ cell transplants and some paediatric autologous stem cell transplants. The Subcommittee noted that this would need further consideration.

7 Amifostine

Application

7.1 The Subcommittee considered an application from a clinician for the funding of amifostine for the prevention of cisplatin related ototoxicity in low and intermediate risk medulloblastoma patients.

Recommendation

7.2 The Subcommittee **recommended** that the application for the funding of amifostine on the Pharmaceutical Schedule be declined. However, The Subcommittee **recommended** that amifostine should be funded for paediatric patients participating in the St Jude's Children's Research Hospital SJMB12 clinical trial.

7.3 The Subcommittee further **recommended** that PHARMAC review the funding mechanisms for unfunded clinical trial treatments for both adult and paediatric clinical trials.

7.4 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; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services and (vi) The budgetary impact (in terms of the pharmaceutical budget and the Government's overall health budget) of any changes to the Pharmaceutical Schedule.*

Discussion

7.5 The Subcommittee noted that the application for the funding of amifostine on the Pharmaceutical Schedule had been reviewed by PTAC at its February 2015 and recommended it be declined. However, members further noted that PTAC had recommended it should be funded for patients participating in a randomised clinical trial sponsored by St Jude's Children's Research Hospital and that PHARMAC review the funding mechanisms for unfunded clinical trial treatments and paediatric oncology treatments.

7.6 The Subcommittee noted that the application was prompted by the applicant wishing to enrol patients into a collaborative group/investigator initiated Phase II study for patients with newly diagnosed medulloblastoma being run by the St Jude Children's Research Hospital Memphis, Tennessee, USA (study SJMB12, clinical trials identifier NCT01878617). Members noted that primary purpose of this study was to identify the risk of recurrence in patients with different clinical risk factors and molecular subtypes and to compare these outcomes with results of a prior St Jude study SJMB03 (Gurney et al; Neuro-Oncology 2014;0:1-8). Members noted that the study was not industry sponsored but included the investigational agent vismodegib, supplied by Roche, and the protocol required that amifostine be administered in conjunction with cisplatin at a dose of 600 mg/m^2 in patients with intermediate and standard risk disease, but not those with high risk disease.

7.7 The Subcommittee noted that medulloblastoma is the most common malignant brain tumour of childhood, and the second most common childhood cancer, members noted that its incidence peaked at around 5-7 years old and it was more common and males compared with females and Maori compared with non-Maori.

7.8 The Subcommittee noted that medulloblastoma was a very aggressive tumour and standard treatment comprised surgery, craniospinal radiation therapy and

platinum based chemotherapy in most patients. Members noted that with these treatments long-term survival is now achieved in approximately three quarters of patients, but treatment was associated with significant toxicity. Members noted that cisplatin was a potent ototoxin and medulloblastoma patients had a high risk of permanent hearing loss when it was combined with craniospinal radiation therapy. The Subcommittee noted that cisplatin-related hearing loss, or impairment, had significant long term quality of life and education implications especially for children. Members noted that whilst there were currently no treatments specifically funded for the prevention of ototoxicity in patients receiving platinum chemotherapy clinical studies of sodium thiosulfate (Doolittle et al Clinical Cancer Research 2001;7:493-500) or intratympanic dexamethasone (Marshak et al Otolaryngology – Head and Neck Surgery 2014;150(6): 983-90) had been conducted, or were underway, and members considered that the results from these interventions were promising.

7.9 The Subcommittee noted evidence supplied by the applicant in support of the application comprised an observational data (Gurney et al; Neuro-Oncology 2014;0:1-8) from St Jude's Children's research hospital of medulloblastoma patients enrolled in two sequential studies SJMB96 and SJMB03 comparing hearing loss in 328 patients who received amifostine with 51 patients who did not. Members noted that the authors reported that among the average-risk medulloblastoma patients amifostine was associated with protection from serious hearing loss (adjusted odd ratio (OR), 0.30; 95% CI, 0.14–0.64) but not in high-risk medulloblastoma patients (OR, 0.89; 95% CI, 0.31–2.54).

7.10 The Subcommittee agreed with PTACs view that the strength and quality of the evidence provided from SJMB96 and SJMB03 was weak noting that combining data from the two trials was questionable given they were unrandomised and undertaken over different time periods.

7.11 The Subcommittee reviewed evidence from two randomised controlled trials of amifostine in children receiving platinum based chemotherapy for hepatoblastoma (Katzenstein et al; Cancer 2009;115:5828-35) and osteosarcoma (Gallegos-Castorena receiving Paed Haem and Onc 2007; 24:403-408). Members noted that neither of these randomised studies demonstrated an ototoxicity protective effect with amifostine.

7.12 The Subcommittee also noted Cochrane review of Medical interventions for the prevention of platinum-induced hearing loss in children with cancer (van As JW, et al. Cochrane Database of Systematic Reviews 2014, Issue 7. Art. No.: CD009219. DOI:10.1002/14651858.CD009219.pub3) which concluded that at present no conclusions can be made about the efficacy of amifostine in preventing ototoxicity in children treated with platinum-based therapy and more high quality research is needed.

7.13 The Subcommittee considered that overall there was insufficient evidence to support the funding of amifostine on the Pharmaceutical Schedule for the prevention of ototoxicity. However, members were supportive of patients being enrolled in collaborative group clinical trials and were supportive of PHARMAC enabling amifostine to be funded for paediatric patients enrolled in the SJMB12 clinical trial.

7.14 The Subcommittee noted that this request for funding of an unfunded treatment in a collaborative group clinical trial setting was similar to other recent funding applications, for example dexrazoxane, and members considered that is was important for PHARMAC to develop a mechanism for funding treatments for non-industry sponsored clinical trials.