

PTAC meeting held 17 & 18 February 2011

(minutes for web publishing)

PTAC minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2008*.

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

PTAC may:

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

Some material has been withheld, in accordance with the Official Information Act 1982 (OIA) to:

- (i) protect the privacy of natural persons (section 9(2)(a));
- (ii) protect information where the making available of the information would be likely to unreasonably prejudice the commercial position of the person who supplied or who is the subject of the information (section 9(2)(b)(ii));
- (iii) protect information which is subject to an obligation of confidence or which any person has been or could be compelled to provide under the authority of any enactment, where the making available of the information would be likely to prejudice the supply of similar information, or information from the same source, and it is in the public interest that such information should continue to be supplied (section 9(2)(ba)(i)); and/or
- (iv) enable PHARMAC to carry on, without prejudice or disadvantage, negotiations (including commercial and industrial negotiations (section 9(2)(j)).

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1 Subcommittee minutes

1.1 Cancer Treatments Subcommittee (CaTSoP) – 19 November 2010

- 1.1.1 PTAC noted CaTSoP's recommendation on lapatinib for HER 2 positive advanced breast cancer and noted that it would be reviewing lapatinib later in the meeting.
- 1.1.2 PTAC noted CaTSoP's recommendation that trastuzumab be funded for patients with HER 2 positive metastatic breast cancer after disease progression following prior adjuvant trastuzumab treatment for early breast cancer. PTAC further noted that CaTSoP considered that the current Special Authority note already covered trastuzumab retreatment and therefore its recommendation would have no financial impact.
- 1.1.3 PTAC disagreed with CaTSoP that the retreatment note in the Special Authority for early breast cancer was adequate, and **recommended** that the trastuzumab Special Authority for early breast cancer be redrafted with renewal criteria.
- 1.1.4 PTAC noted CaTSoP's proposed deferiasirox Special Authority criteria and considered that the criteria allowing patients who have been treated ineffectively with deferiprone and patients intolerant to deferiprone (due to intolerable gastrointestinal side-effects or arthralgia/arthritis) to gain access to deferiasirox are too wide. The proposed criteria could possibly result in a large proportion of patients with congenital inherited anaemias accessing deferiasirox and posing a fiscal risk. PTAC considered that a requirement for a renewal application for oral iron chelators such as deferiprone and deferiasirox should be considered to ensure that the treatments continue to be used only in those for whom they are effective. PTAC **recommended** that CaTSoP review the criteria.
- 1.1.5 The remainder of the record of the meeting was noted and accepted.

1.2 Cardiovascular Subcommittee – 7 October 2010

- 1.2.1 PTAC noted the Cardiovascular Subcommittee's recommendation that prasugrel be listed with medium priority for patients with ST-segment elevation myocardial infarctions (STEMIs) undergoing immediate percutaneous coronary intervention (PCI).
- 1.2.2 PTAC agreed with the recommendation that prasugrel should be listed with medium priority for patients with STEMIs undergoing immediate PCI but further **recommended** that due to the fiscal risk and limited evidence, only one month's therapy should be funded. PTAC considered that it was appropriate to switch patients to clopidogrel after one month.

1.2.3 [

withheld under s9(2)(b)(ii), s9(2)(ba)(i) and/or s9(2)(j) of the OIA

]

1.2.4 The remainder of the record of the meeting was noted and accepted.

1.3 Anti-Infective Subcommittee – 13 October 2010

1.3.1 The record of the meeting was noted and accepted.

2 Pazopanib (Votrient) for advanced and/or metastatic renal cell carcinoma

Application

2.1 The Committee reviewed an application from GlaxoSmithKline (NZ) Ltd for the listing of pazopanib (Votrient) on the Pharmaceutical Schedule for the treatment of patients with advanced or metastatic renal cell carcinoma (RCC).

Recommendation

2.2 The Committee **recommended** that the application be deferred pending phase III comparative evidence becoming available.

2.3 The Committee further **recommended** that the application be referred to its Cancer Treatments Subcommittee for consideration and specific advice regarding the appropriateness of second line use of tyrosine kinase inhibitors in patients with advanced or metastatic renal cell carcinoma (RCC).

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

Discussion

- 2.4 The Committee noted that pazopanib hydrochloride is an orally administered multi-target protein tyrosine kinase inhibitor (TKI) similar to sunitinib (Sutent, Pfizer) and sorafenib (Nexavar, Bayer). The committee noted that sunitinib (Sutent, Pfizer inc) was funded from 1 November 2010 for patients with poor and intermediate prognosis advanced or metastatic RCC. Members noted that the supplier had requested funding for pazopanib under the same criteria as sunitinib as an alternative first line treatment to sunitinib, or as a second line treatment for patients who were intolerant of sunitinib.
- 2.5 The Committee considered that the key evidence for pazopanib was of moderate quality comprising a single randomised, double blind, phase III study comparing pazopanib (800 mg daily) with placebo (study VEG105192, Sternberg et al Journal of Clinical Oncology, 2010 Feb 20;28(6):1061-8.) in treatment-naive and cytokine-pretreated patients with advanced RCC. Members noted that the primary endpoint of the study (progression free survival) PFS was five months longer in patients treated with pazopanib compared with placebo in the overall study population (median, PFS 9.2 v 4.2 months; hazard ratio [HR], 0.46; 95% CI, 0.34 to 0.62; P < 0.0001) and objective response rate was also improved (33% vs 3%). However, members noted that overall survival results were confounded by cross over which occurred in 54% of patients treated with placebo.
- 2.6 The Committee noted that patients reported more adverse events in the pazopanib arm compared with the placebo arm (92% v 74%). Members consider that pazopanib was associated with more diarrhoea, hypertension, hair depigmentation, nausea, weight loss, fatigue, anorexia and transaminase rises. Members further noted that arterial thrombotic events occurred in 3% of pazopanib treated patients compared with none in the placebo arm, haemorrhagic events occurred in 13% of pazopanib treated patients compared with 5% in the placebo arm.
- 2.7 The Committee noted that there was currently no direct comparative evidence of pazopanib with sunitinib (or other TKIs or interferon), however members noted that a randomised Phase III non-inferiority head to head study of pazopanib and sunitinib was underway (VEG10844 COMPARZ) and this study was due for final data collection in May 2011. Members considered that this study would give definitive comparative evidence for pazopanib and sunitinib.
- 2.8 The Committee considered an unpublished two step indirect 'network' comparison conducted by the supplier comparing progression free survival and response rates to pazopanib or sunitinib using evidence from the key pazopanib vs placebo study (VEG105192), a study comparing interferon with medroxyprogesterone acetate (MPA) (Richie et al 1999 Lancet 353 (9146):14-17) and a study comparing interferon with sunitinib (Motzer et al 2009 Journal of Clinical Oncology 27(22): 3584-3590). Members considered that the network analysis was of questionable validity. In particular members considered that there were significant differences between the study populations that made it difficult to interpret the data, and the assumption that MPA was similar to placebo, which could therefore form a 'link' in the analysis was questionable. Members considered that it was appropriate to wait until the comparative clinical evidence was available prior to drawing any conclusions regarding the relative efficacy and safety of pazopanib and sunitinib.
- 2.9 The Committee noted that the supplier had requested funding for pazopanib as an alternative to sunitinib, or after sunitinib in patients who were intolerant to sunitinib. Members considered that in principle competition in the TKI market was welcome but

noted that the current Special Authority criteria for sunitinib would need to be amended for such funding to be implemented otherwise it would be likely that sunitinib would be used as a second line treatment after failure of pazopanib, or vice versa. Members considered that although there was no evidence to support the use of a second-line TKI inhibitor some clinicians are likely to want to try subsequent lines of TKI therapy in patients with advanced RCC as this approach was being used in other settings overseas; for example use of lapatinib following failure of trastuzumab, or continuing trastuzumab despite disease progression. Members also considered that funding a second TKI following intolerance to a first TKI appeared to be a reasonable option, but considered it would likely result in significant slippage with patients accessing a second TKI following disease progression on a first.

3 Trastuzumab (Herceptin) for HER2 positive metastatic gastric cancer

Application

- 3.1 The Committee reviewed an application from Roche Products (NZ) Ltd for funding of trastuzumab (Herceptin) on the Pharmaceutical Schedule to be widened to include treatment of patients with locally advanced or metastatic gastric cancer or gastro-oesophageal junction tumours, exhibiting high levels of HER 2 positivity (IHC 2+/ISH+ or IHC 3+) in combination with capecitabine or 5FU and platinum based chemotherapy.

Recommendation

- 3.2 The Committee **recommended** that trastuzumab, in combination with capecitabine or 5FU and platinum based chemotherapy, should be funded for treatment of patients with locally advanced or metastatic gastric cancer or gastro-oesophageal junction tumours, exhibiting high levels of HER 2 positivity (IHC 2+/ISH+ or IHC 3+). Members gave this recommendation a low priority.
- 3.3 The Committee further **recommended** that the application be referred to its Cancer Treatments Subcommittee for consideration and specific advice regarding appropriate Special Authority criteria and inputs for cost utility analysis.

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

Discussion

- 3.4 The Committee considered that relevant cancers for this topic encompass adenocarcinomas of the stomach (including cardia), gastro-oesophageal junction (GEJ)

and lower one third of the oesophagus. Members noted that the epidemiology of gastric cancer was changing, with historically known risk factors (e.g. *Helicobacter pylori* infection, autoimmune atrophic gastritis and diets high in smoked, pickled and salted foods) being supplanted by increased incidence of GEJ malignancies associated with obesity and gastroesophageal reflux disease (GORD).

- 3.5 The Committee noted that trastuzumab, a humanised monoclonal antibody targeted against HER2 (Human Epithelial Growth Factor Receptor 2), was initially developed for treatment of breast cancer, where around a quarter of tumours overexpress HER 2, but it may also be relevant in gastric cancers where HER 2 overexpression is evident in up to a third of patients. Members noted that trastuzumab is currently funded for patients with early stage or metastatic HER 2 positive (IHC 3+ or (F)ISH+) breast cancer.
- 3.6 The Committee noted that there are approximately 351 new cases of gastric cancer registered in New Zealand each year, the majority of which (around 60%) occur in men. Members further noted that Māori and Pacifica peoples have 3-4 higher incidence of gastric cancer compared with NZ Europeans.
- 3.7 The Committee considered that currently most New Zealand patients with advanced gastric cancer would receive triple combination chemotherapy, mainly epirubicin, cisplatin and capecitabine (ECX).
- 3.8 The Committee reviewed key evidence for trastuzumab comprising a single open label, phase III study comparing trastuzumab plus chemotherapy or chemotherapy alone in 594 patients with HER 2 positive inoperable locally advanced or metastatic gastric or GEJ cancer (Trastuzumab for Gastric Cancer (ToGA) study) (Bang et al. Lancet 2010;376:687-97). Members noted that chemotherapy comprised capecitabine plus cisplatin (CX) or fluorouracil plus cisplatin (CF) (chosen at the investigator's discretion) given every three weeks for up to six cycles. Trastuzumab was given by intravenous infusion at a dose of 8 mg/kg on day 1 of the first cycle, followed by 6 mg/kg every three weeks until disease progression, unacceptable toxicity, or withdrawal of consent. Members further noted that crossover to trastuzumab for chemotherapy-only patients at the time of disease progression was not permitted. The Committee considered the evidence to be of moderate strength and quality
- 3.9 The Committee noted that after a median follow-up of 18.6 months in the trastuzumab plus chemotherapy group and 17.1 months in the chemotherapy alone group, median overall survival (OS, the primary endpoint) was significantly improved in the trastuzumab treated patients (13.8 months vs. 11.1 months hazard ratio (HR) 0.74; 95% CI 0.60–0.91; p=0.0046). Members further noted that median progression-free survival (PFS) was also significantly improved at 6.7 months vs. 5.5 months (HR 0.71, 95% CI 0.59–0.85; p=0.0002) as were other secondary endpoints. However, members noted that there was no distinguishable difference in quality of life between the two treatment groups and questioned the clinical relevance of the small improvements in overall survival (2.7 months) and progression free survival (1.2 months) seen.
- 3.10 The Committee noted that trastuzumab was associated with a slightly higher rate of grade 3 diarrhoea but that there was no difference in incidence of cardiac adverse events (6% on both treatment groups). Members noted however that there was negligible prior anthracycline exposure in these patients.

- 3.11 The Committee noted that a pre-planned subgroup analysis found variable survival in subgroups of the ToGA study with different levels of HER 2 expression. Members further noted results from an unplanned post-hoc exploratory analysis demonstrated that overall survival was increased by 4.2 months in patients with 'high' HER 2 expression (defined as IHC 2+/FISH positive or IHC 3+). However, members were concerned about the validity of this result, noting that an unknown number of post-hoc analyses had been undertaken on the data and the methodology for repeated subgroup analyses was not clear. Therefore, members considered that it was possible that the apparent increased benefit shown in the subgroup defined, and proposed for funding, could simply be a result of chance arising from multiple post-hoc analyses.
- 3.12 The Committee considered that the suppliers estimate of the patient numbers who may be eligible for funding, based on the overall incidence of 'high' HER 2 expression in the entire population enrolled in the ToGA study (16.6%) may be too low. Members noted that 33% of the Australian patients enrolled in ToGA had 'high' HER 2 expression and considered that to be more representative of the likely prevalence in New Zealand.
- 3.13 Overall the Committee considered that trastuzumab provided a modest benefit in patients with HER 2 positive metastatic gastric cancer. Members noted that trastuzumab was an expensive treatment and that the suppliers own cost utility analysis showed that trastuzumab was likely to be relatively cost-ineffective compared with other currently funded treatments and some other treatments awaiting funding.

4 Lapatinib (Tykerb) for HER2 positive metastatic breast cancer

Application

- 4.1 The Committee reviewed an application from GlaxoSmithKline (NZ) Ltd for listing of lapatinib (Tykerb) on the Pharmaceutical Schedule as an alternative to trastuzumab in patients presenting with HER 2 positive metastatic breast cancer (mBC) (first-line) and as a treatment for women with HER 2 positive mBC patients who have already been treated with trastuzumab in the metastatic setting and in whom disease has progressed (second-line).

Recommendation

- 4.2 The Committee **recommended** that lapatinib, in combination with an aromatase inhibitor or paclitaxel, should be funded as an alternative to trastuzumab for the first line treatment of patients presenting with HER 2 positive metastatic breast cancer. Members gave this recommendation a medium priority.
- 4.3 The Committee further **recommended** that the application for first line mBC as an alternative to trastuzumab be referred to its Cancer Treatments Subcommittee for consideration and specific advice regarding appropriate Special Authority criteria.
- 4.4 The Committee **recommended** that the application for the funding of lapatinib as a second line treatment in women with HER 2 positive mBC patients following disease progression on trastuzumab be declined.

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

Discussion

- 4.5 The Committee noted that it had previously considered applications from the supplier and the Association of New Zealand Cancer Specialists – Breast Special Interest Group for the funding of lapatinib for the treatment of patients with HER 2 positive metastatic breast cancer (mBC) following trastuzumab failure (second line). The Committee noted that at its most recent review (November 2010) it had recommended the application for this population be declined.
- 4.6 The Committee noted that the supplier had provided a vast number of papers as evidence in support of its application but noted that the majority had already been reviewed by PTAC and/or its Cancer Treatments Subcommittee on previous occasions. Members considered that there was little new evidence provided in the application.
- 4.7 The Committee reviewed key evidence from three studies for the use of lapatinib as a first line treatment in patients with HER 2 positive mBC in combination with an aromatase inhibitor (letrozole) or a taxane (paclitaxel). Members noted only two of the studies had been published; EGF30001 (Di Leo et al J Clin Oncol 2008, Sherril et al Curr Med Res Opin. 2010) and EGF30008 (Johnston et al J Clin Oncol 2009 and Schwartzberg et al J Clin Oncol 2010). Members noted that evidence from the 3rd study, which was ongoing, comprised a Clinical Study Report (EGF104535).
- 4.8 The Committee noted that study EGF30001 was a randomised phase III study comparing lapatinib (1500 mg once daily) plus paclitaxel (175 mg/m² every three weeks) with placebo plus paclitaxel as first-line treatment for patients with metastatic breast cancer of either negative HER2 disease or unknown HER2 status. Members noted that efficacy analyses were repeated in retrospectively defined HER2 positive populations which resulted in low patient numbers (lapatinib n=49, placebo n=37). Members noted that in this subgroup median time to progression was significantly improved in the lapatinib treated patients (36.4 weeks vs 25.1 weeks HR 0.53, 95% CI 0.31 – 0.89, p=0.005) but there was no statistically significant difference in overall survival (OS). Members considered that this was a small study and therefore results needed to be confirmed in a larger study.
- 4.9 The Committee noted that study EGF30008 was a randomised phase III study comparing lapatinib (1500 mg once daily) plus letrozole (2.5 mg once daily) with letrozole plus placebo as first-line treatment of postmenopausal hormone receptor–positive metastatic breast cancer patients, including a population with known HER2 positive disease (lapatinib n=111, placebo n=108). Members noted that after a median follow-up of 1.8 years progression free survival (PFS), the primary endpoint, was significantly improved in the lapatinib treated patients compared with placebo (8.2 months vs. 3.0 months HR 0.71, 95% CI 0.53 – 0.96, p=0.019), overall response rate was higher in the

lapatinib treated patients (28% vs 15%) but there was no statistically significant difference in overall survival although median OS had not been met in either arm.

- 4.10 The Committee noted that EGF104535 was an ongoing randomised phase III study comparing lapatinib (1500 mg once daily) plus paclitaxel (80 mg/m² weekly) (n=222) with placebo plus paclitaxel (n=222) as first-line treatment for patients with HER 2 positive metastatic breast cancer. Members noted that on disease progression patients in the placebo arm were permitted to cross over to lapatinib and patients on lapatinib were permitted to receive other biological agents. The Committee noted that PFS was significantly improved in patients treated with lapatinib (9.7 months vs 6.5 months HR 0.52, 95% CI 0.42 – 0.64, p=<0.0001), members further noted that OS was also improved (27.8 months vs. 20.5 months) but considered that interpretations of overall survival benefits were confounded by the permitted cross over.
- 4.11 The Committee considered that overall the evidence demonstrated that the addition of lapatinib to standard first line mBC treatments (letrozole or paclitaxel) improved disease outcomes. Members considered that lapatinib treatment is associated with an increased incidence of diarrhoea, rash and neutropaenia.
- 4.12 The Committee noted that in the first line setting lapatinib was currently indicated for use only in combination with letrozole, based on the EGF30008 study, but that the supplier had indicated that it intends to file an application to Medsafe for its use in combination with paclitaxel, based on EGF104535) in early 2011.
- 4.13 The Committee noted that there was no new evidence presented for the use of lapatinib as a second line treatment following disease progression on trastuzumab; members considered that the main evidence in this patient population remained that from study EGF100151 (Geyer et al NEJM 2006; Cameron et al Breast Cancer Res Treat 2008) which the Committee had reviewed on a number of previous occasions. The Committee reiterated its view that in the second line setting lapatinib offered only modest benefits in terms of delaying disease progression, without any survival advantage.
- 4.14 The Committee noted that there was no evidence from head to head studies comparing lapatinib with trastuzumab in the mBC setting. Members noted that a head to head study was ongoing but this was in the adjuvant early breast cancer setting.
- 4.15 The Committee reviewed an unpublished indirect meta-analysis comparing trastuzumab with lapatinib conducted by the supplier. Members noted that seven studies were included in the meta-analysis (three lapatinib studies, four trastuzumab studies). Members also noted that all of the trastuzumab studies and two of the lapatinib studies enrolled first line metastatic breast cancer patients, however, one of the lapatinib studies included patients who had previously failed trastuzumab treatment (second line, Cameron et al) and this comprised the largest study population for lapatinib. Members further noted that the studies used different comparator treatments comprising various chemotherapy and hormonal treatments and not all studies reported the same endpoints. Members also noted that EGF104535 was not included in the meta-analysis but the supplier had indicated that it would update the analysis to include this evidence.
- 4.16 The Committee noted that the meta-analysis appeared to be based on one previously published (Amir et al 2010), the only difference being the addition of trastuzumab studies. Members noted that the Amir study was not referenced. Members considered

that because of major study heterogeneity it was not possible to draw meaningful conclusions regarding the relative efficacy of lapatinib and trastuzumab from the meta-analysis.

- 4.17 The Committee noted that trastuzumab was currently funded for patients with HER 2 positive mBC. Members considered that the main advantages of lapatinib compared with trastuzumab was that it was an oral treatment and since it crossed the blood brain barrier it may provide some additional benefits for patients with brain metastases, although there was limited evidence to support this. Members considered it reasonable to limit patients to receive either lapatinib or trastuzumab in the mBC setting, but noted this may be difficult to implement as it was likely that clinicians would want to use trastuzumab following disease progression on lapatinib or vice versa. However, members noted that there was no evidence for the use of trastuzumab following lapatinib and it did not support the funding of lapatinib following trastuzumab.
- 4.18 The Committee reiterated its previous view that studies of lower doses of lapatinib taken with food should be undertaken.

5 Alglucosidase alfa for late onset Pompe disease

Application

- 5.1 The Committee reviewed an application from PHARMAC, in response to an application to the Community Exceptional Circumstances Scheme, for alglucosidase alfa (Myozyme) for long term enzyme replacement therapy in patients with late-onset Pompe's disease (GAA deficiency).

Recommendation

- 5.2 The Committee **recommended** that the application be declined.

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

Discussion

- 5.3 The Committee reviewed evidence from the Van der Ploeg et al study (NEJM 2010, 362; 15: 1396-1406) of alglucosidase alfa in late-onset Pompe's disease. Members noted this was a 78 week double blind placebo controlled study of 90 patients with late-onset Pompe disease. Members noted that at 78 weeks patients randomised to alglucosidase alfa walked an additional 28 meters on average in the six minute walk test (6MWT) (p=0.03) and had an absolute increase of 3.4 percentage points in forced vital capacity (FEV₁) (p=0.006) compared with those randomised to placebo. Members noted that there was no statistically significant difference between the two groups in the SF-36 physical component summary.

- 5.4 The Committee noted that trials of treatments for Chronic Obstructive Pulmonary Disease (COPD) typically use improvements of 50 meters to demonstrate clinically significant improvements, and that the data provided in the Van der Ploeg et al study would suggest that very few patients would show this level of improvement. Members questioned the clinical significance of the results as a measure of therapeutic outcome of therapy.
- 5.5 The Committee noted the risk of anaphylaxis or allergic reaction to alglucosidase therapy, with 5% of patients on alglucosidase alfa having an anaphylactic reaction. The Committee also noted that the antibodies that inhibited enzyme uptake occurred in 18 of the 60 patients (31%) receiving alglucosidase alfa.
- 5.6 Members noted that the improvement compared to placebo occurred in the initial 26 weeks of therapy and the separation remained almost parallel from then on for most of the outcome variables studied. Members considered that this may result in no long term improvements with prolonged usage. Members noted that the results should be regarded as preliminary and hypothesis generating only and that a longer follow-up would be needed to confirm long-term improved clinical outcomes in this patient population. Members considered this view was consistent with the statement by the authors in the study in the NEJM that “longer-term study of alglucosidase alfa in children and adults with Pompe’s disease would be needed to understand fully the potential of treatment.”
- 5.7 The Committee noted that there was no currently funded therapy available to alter the enzyme basis of Pompe disease. Members noted that supportive therapy remained available such as ventilation.
- 5.8 The Committee considered that there was no evidence for improved outcomes for patients with late-onset Pompe disease who were treated with alglucosidase alfa, and that the evidence presented at best provided proof-of-concept of some clinical impact. Members noted that alglucosidase alfa was extremely expensive and did not show any meaningful clinical outcomes at this time.

6 Mycophenolate mofetil for severe atopic eczema

Application

- 6.1 The Committee reviewed an application from a clinician for the listing of mycophenolate mofetil (Cellcept, Myaccord) on the Pharmaceutical Schedule for the treatment of severe, treatment-refractory atopic eczema.

Recommendation

- 6.2 The Committee **recommended** that mycophenolate mofetil may be used to treat patients with severe, treatment-resistant atopic eczema under the current Special Authority as cyclophosphamide may be considered to be contraindicated for this indication.

The Decision Criteria particularly relevant to this recommendation are: (i) *The health needs of all eligible people within New Zealand;* (iii) *The availability and suitability of*

existing medicines, therapeutic medical devices and related products and related things; (iv) The clinical benefits and risks of pharmaceuticals; (v) The cost-effectiveness of meeting health needs by funding pharmaceuticals rather than using other publicly funded health and disability support services.

Discussion

- 6.3 The Committee noted that the application had been prompted by applications for the use of mycophenolate mofetil (MMF) in the treatment of severe treatment-refractory atopic eczema being declined by the Hospital Exceptional Circumstances (HEC) and Community Exceptional Circumstances (CEC) panels. Members noted that seven dermatologists had made 10 applications on behalf of eight patients over the past five years. One had been approved and seven declined through CEC. One which had previously been declined through CEC was approved through HEC as the cost of treatment with MMF per annum was less than the cost of the hospital admissions for this patient in any one year. One other application through HEC had been declined.
- 6.4 The Committee noted that mycophenolate mofetil (MMF) is currently funded, subject to Special Authority, for treatment of transplant recipients or patients with diseases where steroids and azathioprine have been trialled and discontinued and cyclophosphamide is either discontinued because of unacceptable side effects or an inadequate clinical response or is contraindicated. The Committee noted that while MMF is only indicated for prophylaxis of acute organ rejection it is increasingly being used “off-label” in a wide range of other diseases. Applications through Exceptional Circumstances had prompted widening of access as defined by the current criteria.
- 6.5 The Committee noted that first line treatments of eczema include soap substitutes, emollients, topical steroids and antibiotics if infected. Short term use of oral steroids is required for flare-ups. Members noted that, for those patients with eczema resistant to these therapies, topical tacrolimus or pimecrolimus, UV phototherapy or systemic agents such as cyclosporine followed by methotrexate, azathioprine and interferon are considered. Members noted that there had been no recent reports of cyclophosphamide use in patients with severe eczema although there was a 1978 article (Morrison, J.G.L. and Schulz, E.J. (1978), Treatment of eczema with cyclophosphamide and azathioprine. British Journal of Dermatology, 98: 203-207) where nine patients with severe eczema who had not responded satisfactorily to systemic and topical corticosteroid therapy were treated with cyclophosphamide and azathioprine. Several months treatment was needed to obtain significant improvement and long term remissions followed cessation of therapy. The Committee noted that it could be argued that patients with severe eczema resistant to steroids and azathioprine would meet the current Special Authority for MMF as cyclophosphamide could be deemed as contraindicated.
- 6.6 The Committee reviewed the evidence provided by [withheld under s 9(2)(a) of the OIA], sourced by PHARMAC and by one of the Committee members. The Committee noted that MMF has been shown to be effective in the treatment of severe, resistant atopic eczema and dermatitis in adults and children. The Committee considered that the quality of the available evidence was low to moderate as it consisted of small, uncontrolled, non-randomised, and prospective or retrospective studies and predominately in an adult population.

- 6.7 The Committee noted one retrospective analysis (Heller et al. Mycophenolate mofetil for severe childhood atopic dermatitis: experience in 14 patients. *Br J of Dermatol.* 2007; 157:127-132) reporting the use of MMF in children aged two to 16 years (treatment periods ranged from 2-24 months at a dose range of 400-3000 mg per day). The mean time to response was four weeks with four patients having complete clearance, four had a 90% improvement; five patients had a 60-90% improvement and one patient had an inadequate response. MMF was well tolerated with no significant adverse events.
- 6.8 The Committee reviewed a number of other studies including Neuber K. et al. Treatment of atopic eczema with oral mycophenolate mofetil *Br J Dermatol.* 2000;143;385-391; Grundmann-Kollman M. et al. Mycophenolate mofetil is effective in the treatment of atopic dermatitis. *Arch dermatol* 2001;137:870-873; Murray M.L. and Cohen J.B. Mycophenolate mofetil therapy for moderate to severe atopic dermatitis. *Clin Exp Dermatol* 2006;32:23-37. Ballester I. et al. Severe Atopic Dermatitis: Treatment with mycophenolate mofetil in eight patients. *Actas Dermo-Sifiliograficas* 2009; 100:883-7; Jackson J.M. et al Mycophenolate mofetil for the treatment of chronic dermatitis: an open label study of 16 patients. *J Drugs Dermatol* 2010; 9(4):356-62 and van Velsen S.G.A. et al First experience with enteric-coated mycophenolate sodium (Myfortic) in severe recalcitrant adult atopic dermatitis: an open label study. *Br J Dermatol* 2009; 160(3):687-91. Patients aged 15-81 years were treated with an average of 1 to 2 g MMF per day (maximum 3g/day) for periods between four weeks and 200 weeks. Changes in the SCORAD index were used to measure the effectiveness of MMF. In total, 64 out of 74 patients in the reviewed studies responded to treatment with MMF with the majority having complete or near complete remission allowing for dose reduction. MMF was well tolerated. Adverse events that were reported included: insomnia (2 patients), mild nausea (1), grade 1 thrombocytopenia (1), herpes retinitis (1), herpes zoster (4), staphylococcal infections (2), folliculitis (3), and palpitations (1). All adverse events responded to appropriate treatment (anti-virals, antibiotics, reduction in MMF dose etc).
- 6.9 The Committee noted that [withheld under s 9(2)(a) of the OIA] had estimated that the 30 to 35 Dermatologists in New Zealand may have one or two patients that would benefit from treatment with MMF and that of these patients, approximately 70% may remain on treatment for two to five years. The Committee considered that this may be an over estimation of patient numbers, considering there had only been 10 applications to CEC and/or HEC in the past five years. The Committee noted that while MMF would be used in combination with soap substitutes, emollients, topical steroids and possible oral steroids, there may be a reduction in the use of cyclosporine and/or steroid use and to a lesser extent methotrexate and azathioprine.

7 Ivermectin for crusted scabies

Application

- 7.1 The Committee considered a request from a clinician to list ivermectin tablets for first line treatment of crusted scabies outbreaks in institutional settings.

Recommendation

- 7.2 The Committee **recommended** that ivermectin be funded for the treatment of crusted scabies and in those for whom it is not possible to use lotions or creams.
- 7.3 The Committee further **recommended** that PHARMAC staff discuss with the Ministry of Health the possibility of making outbreaks of scabies in institutional settings a notifiable disease. If this were possible the decision to allow funded access would be made by the Medical Officer of Health. Under this scenario a Special Authority would be unnecessary; therefore, the Committee deferred making a final recommendation until further information was available.

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; and (vii) The direct cost to health service users*

Discussion

- 7.4 The Committee noted that scabies outbreaks were a significant problem in institutional settings due to the difficulties and time involved in applying topical treatments and the difficulty in isolating residents, and this was particularly so in institutions with elderly residents and dementia patients. The Committee also noted that there are more likely to be unrecognised cases of crusted scabies in institutional settings, particularly amongst residents that may be immunocompromised and this is a major source of re-infestation.
- 7.5 The Committee noted that ivermectin is registered by Medsafe for the treatment of human sarcoptic scabies after prior treatment has failed. The recommended dosage is a single oral dose to provide ivermectin 200mg/kg of body weight. In the heavily infected forms of profuse or crusting scabies, a second dose within eight to 15 days of ivermectin and/or concomitant topical therapy may be necessary to obtain recovery. The Committee noted that the application was for use of ivermectin as a first line treatment for crusted scabies and for the treatment of residents in institutional settings with scabies infections or probable scabies infections. The applicant was requesting the use of two doses of ivermectin for each patient to ensure eradication of scabies in all residents. The applicant had suggested that more than two doses of ivermectin along with topical treatment may be required to eradicate scabies in people with crusted scabies.
- 7.6 The Committee noted that evidence of efficacy for this indication is limited and is mostly comprised of expert opinion supported by small uncontrolled studies. The Cochrane Review (Interventions for treating scabies, the Cochrane Library 2010 Issue 10) gives a comprehensive review of all topical and oral agents used for treating scabies. This reviewed 21 studies with treatment failure as the outcome measure. The review concluded that topical permethrin appears to be the most effective treatment for scabies and that ivermectin appears to be an effective oral treatment. The review further stated that more research is needed especially for the management of scabies in institutions.
- 7.7 The Committee also noted the results of an RCT comparing ivermectin with permethrin (Usha V et al. A comparative study of oral ivermectin and topical cream in the treatment of scabies. J.Am.Acad Dermatol 2000; 42:236-40) of 85 patients (40 receiving ivermectin; 45 receiving a single dose of permethrin) with follow-ups at one, two, four and eight weeks. A single dose of ivermectin gave a cure rate of 70% which increased to

95% with two doses at a two week interval. A single dose of permethrin was effective in 97.8% of patients with an additional patient responding to a second application. The two patients who did not respond to ivermectin were crossed over to the permethrin group and were cured after a single application. No major side effects were observed in either group. The authors concluded that a single application of permethrin is superior to a single dose of ivermectin and similar to two doses of ivermectin taken two weeks apart.

- 7.8 The Committee noted that in terms of safety ivermectin has been widely used and even with repeated doses serious adverse effects have been rare (Cochrane Review 2010). A letter to the Lancet (Barkwell R, Shields S. Deaths associated with ivermectin treatment in scabies. Lancet 1997; 349(9059):1144-5) reported an increased number of deaths amongst dementia care patients who had been unsuccessfully treated with up to three topical agents. 15 of the 47 patients died over a six month period compared to five in a “matched” control group. Whether this was due to ivermectin or to interactions with other scabicides, including lindane and permethrin, or other treatments such as psychoactive drugs was not clear, and there was considerable discussion in the Lancet of the validity of the report at that time. The Committee noted veterinary reports that collie dogs are known to be particularly prone to ivermectin neurotoxicity. There is speculation that increased crossing of the blood brain barrier by ivermectin could account for an increase in side-effects in the elderly.
- 7.9 The Committee considered that there was a public health dimension to outbreaks of scabies in institutions. Elderly and immunocompromised patients are more likely to have crusted scabies and there may be issues with the capacity for patients to give informed consent, particularly the elderly, dementia and intellectually disabled patients. The Committee considered that crusted scabies may need to be a notifiable disease and have a team approach to treatment involving the local Medical Officer of Health, a dermatologist, and medical, nursing and ancillary staff at the institution.
- 7.10 The Committee noted that ivermectin should be available for treatment but there were a number of areas that needed clarification prior to listing on the Pharmaceutical Schedule. These include, among others, the definition of institution in which treatment with ivermectin may be appropriate; definition of ‘outbreak’ in an institution, whether only individuals with crusted scabies should be treated or whether all residents and staff should also be treated. The Committee considered that guidelines could be developed in discussion with the Ministry of Health, dermatologists and infectious disease specialists.
- 7.11 The Committee noted that, currently, the cost of treatment with ivermectin is significantly higher than topical treatment and is carried by the patient, the institution or the family. The Committee recognised that there is considerable time required for staff to treat patients topically. The Committee noted that restrictions on the use of ivermectin may be required to contain costs.

8 Tiotropium bromide for chronic obstructive pulmonary disease

Application

- 8.1 The Committee reviewed an application from Boehringer Ingelheim for:

- 8.1.1 Widening of access to the listing of tiotropium bromide (Spiriva) on the Pharmaceutical Schedule for the treatment of Chronic Obstructive Pulmonary Disease (COPD), and
- 8.1.2 Inclusion of a spirometry requirement for all respiratory treatments (particularly long-acting inhaled beta agonists (LABAs), inhaled corticosteroids (ICS) and LABA-ICS combinations), or, alternatively, the elimination of the Special Authority for tiotropium bromide.

Recommendation

- 8.2 The Committee **recommended** that the Application for widening access to tiotropium bromide be declined.

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

- 8.3 The Committee **recommended** the Application for the inclusion of a spirometry requirement for all respiratory treatments (particularly LABAs, ICS and LABA-ISC combinations), or alternatively the elimination of the Special Authority for tiotropium bromide, be declined.

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 in 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

- 8.4 The Committee noted that tiotropium bromide is currently funded, subject to Special Authority criteria, as treatment for COPD patients who have met certain eligibility criteria including an FEV₁ <60% of predicted and the absolute FEV₁. The Committee noted that the current GOLD classification of COPD stage is: stage I Mild FEV₁ ≥ 80%; stage II Moderate FEV₁ 50 – 79%; stage III Severe FEV₁ 30 – 49%; stage IV Very severe FEV₁ <30%.
- 8.5 The Committee noted that the clinical evidence for widening the eligibility criteria to above an FEV₁ of 60% was of modest strength and quality. The Committee noted that the application largely used subset analysis of the UPLIFT (Understanding Potential

Long-term Impacts on Function with Tiotropium) study, a large multi-centred trial supported by Boehringer Ingelheim and Pfizer (Tashkin et al N Engl J Med 2008; 359:1543-1554). The UPLIFT trial recruited 5993 patients with a mean FEV₁% predicted of ~ 47% from secondary care facilities in 37 countries including a study site in Auckland. Patients were randomised to tiotropium 18 mg per day or placebo and any short term muscarinic antagonists (SAMA, mostly ipratropium) were discontinued. All other respiratory medications (short-acting inhaled beta agonists (SABA), ICS, LABA, LABA/ICS combinations) were freely prescribed, and in this respect the study reflected typical COPD patients in specialist practice. The Committee noted that, despite the power of this study, there was no detectable difference in the primary endpoint of deterioration of lung function as measured by the rate of FEV₁ decline, which remained at 40 – 42 ml per year in each group, and that overall the results were questionable in terms of clinical benefit.

- 8.6 The Committee noted results from the pre-specified subgroup analysis from the UPLIFT trial were reported by Decramer et al (Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a pre-specified subgroup analysis of a randomised controlled trial. Lancet 2009;374:1171-1178); Troosters et al (Tiotropium as a first maintenance drug in COPD: secondary analysis of the UPLIFT trial. Eur Respir J 2010; 36: 65-73); and Tashkin et al (Efficacy of tiotropium in COPD patients with FEV₁ ≥ 60% participating in the UPLIFT Trial. Poster, ERS 2010, Barcelona Spain).
- 8.7 The Committee noted that these subgroup analysis of the UPLIFT trial focussed on GOLD stage II patients, defined as moderate with FEV₁ levels 50-79%. The Committee noted that while some of the results of these studies were statistically significant they were not necessarily clinically significant. The Tashkin study showed a modest reduction in the risk of exacerbation.
- 8.8 Members noted that the overall UPLIFT trial (Tashkin NEJM 2008) was stated to have been sufficiently powered to allow for pre-planned subgroup analysis on a number of clinical variables, including severity of disease. However, according to the detail in Appendix six of the main report, which had been accessed by Committee members (only available in pages 72-74/77 on the NEJM website at http://www.nejm.org/doi/suppl/10.1056/NEJMoa0805800/suppl_file/nejm_tashkin_1543s_a1.pdf), the initial reporting of subgroup results by COPD severity had combined GOLD stages I and II and that in both analyses the subgroup treatment interaction values did not reach statistical significance. Members considered that these results indicated no evidence of a different treatment effect between stages I and II disease combined and other categories of disease severity (with p-values for the interaction terms of 0.19 and 0.08 for pre- and post-bronchodilator FEV₁ declines), and that this likely rendered the subsequent further subgroup analyses by COPD severity invalid. Members also noted that this important information was not stated in the Decramer Lancet or Troosters ERJ publications of UPLIFT subgroup analyses for GOLD stage II patients.
- 8.9 The Committee noted some first results from the POET-COPD trial (Vogelmeier et al (Reductions in COPD Exacerbations with tiotropium compared to salmeterol - the POET-COPD trial. Poster, ERS 2010, Barcelona Spain), which is a head to head trial of tiotropium versus salmeterol in moderate to severe (FEV₁ < 50%) COPD finding to date a 28% reduction in exacerbations severe enough for hospitalisation. The Committee noted that peer review and publication of these preliminary results is yet to come.

- 8.10 The Committee noted treatment guidelines from NICE, GOLD, the Canadian Thoracic Society and the Thoracic Society of Australia and New Zealand (TSANZ). The Committee noted that spirometry was a necessary diagnostic tool for COPD and that access to spirometers in clinical practice should now be adequate. The Committee considered that the current Special Authorities are appropriate, that the requirement to offer smoking cessation counselling was a crucial part of the Special Authority for tiotropium and as such the access criteria should remain unchanged.
- 8.11 The Committee noted that spirometry was a useful tool in the management of patients with COPD using inhaled corticosteroids and long-acting beta agonists; however, it considered that it would be difficult to incorporate this into current Special Authorities.

9 Atropine 0.5% eye drops for paediatric patients

Application

- 9.1 The Committee reviewed a paper from PHARMAC staff in relation to the use of atropine 0.5% eye drops in paediatric patients.

Recommendation

- 9.2 The Committee **recommended** that atropine 0.5% eye drops be made available either through Exceptional Circumstances (EC) or listed with high priority on the Discretionary Community Supply (DCS) list for use in paediatric patients for congenital cataract surgery.

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 and (iv) The clinical benefits and risks of pharmaceuticals.*

Discussion

- 9.3 The Committee noted that PHARMAC has received correspondence from [withheld under s 9(2)(a) of the OIA] highlighting the need for atropine 0.5% eye drops to be available funded for paediatric patients as the 1% strength which is available on the Pharmaceutical Schedule was inappropriate. The Committee noted that this was in response to the minute by the Ophthalmology Subcommittee at their May 2010 meeting that atropine 1% eye drops could be used in paediatric patients by dabbing away the excess. The Committee also noted that the Ophthalmology Subcommittee also suggested cyclopentolate hydrochloride 1% as an alternative treatment.
- 9.4 The Committee noted that atropine eye drops are mainly required in children requiring cataract surgery and surgery is usually done for inborn cataracts between four and eight weeks of age. The Committee noted that there have been 11 Hospital Exceptional Circumstances (HEC) applications for atropine 0.5% eye drops in paediatric patients over the last three years. The Committee also noted that atropine 0.5% eye drops is not

registered in New Zealand and is currently being imported from Australia through a wholesaler.

- 9.5 The Committee considered that there was limited clinical evidence available to address this issue of safety of atropine 1% in paediatric patients except old non-randomised controlled trials (RCTs). The Committee considered that paediatric patients were more susceptible to the systemic effects of atropine namely; flushing, irritability, respiratory depression, tachycardia and arrhythmias as highlighted by [withheld under s 9(2)(a) of the OIA]. The Committee considered that it was inappropriate to use atropine 1% eye drops in paediatric patients and just dab away the excess.
- 9.6 The Committee considered that it was appropriate that atropine 0.5% be used instead of the 1% eye drops in paediatric patients for safety reasons. The Committee considered that possible alternatives were cyclopentolate 0.5% eye drops but it has a shorter duration of action and is not listed on the Pharmaceutical Schedule. The Committee considered that atropine 0.5% eye ointment was also a suitable alternative but carried the same risk of systemic side-effects as the eye drops. It was also not available in New Zealand.
- 9.7 The Committee considered that it was appropriate for atropine 0.5% to continue to be accessed for paediatric patients through EC due to the small patient numbers. The Committee considered that listing atropine 0.5% eye drops on the Discretionary Community Supply list for this patient group was also another option.

10 Clodronate (Ostac) for osteoradionecrosis

Application

- 10.1 The Committee reviewed an application from a clinician for the listing of clodronate (Ostac) on the Pharmaceutical Schedule for the treatment of patients with osteoradionecrosis.

Recommendation

- 10.2 The Committee **recommended** that the application for the funding of clodronate for the treatment of patients with osteoradionecrosis be declined.

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.*

Discussion

- 10.3 The Committee noted that radiation therapy-associated osteonecrosis of the jaw had incidence rates between 5% and 15% according to review articles (Nabil et al. Int J Oral

Maxillo Surg. 2011 Mar; 40(3):229-43. Epub 2010 Nov 5). The Committee considered that Māori and Pacific people would probably be at a higher risk of head and neck cancers due to their higher rates of tobacco smoking. The Committee also noted that osteonecrosis is difficult to treat with no particular satisfactory rapid-acting therapy.

- 10.4 The Committee considered that depending on severity, current available treatments include preventative measures such as dental evaluation and therapy prior to radiotherapy, mouth hygiene, antibiotics, hyperbaric oxygen and surgery. The Committee considered that there was no evidence to support the efficacy of hyperbaric oxygen and it may be harmful. The only randomised controlled trial (RCT) identified (Annane et al. J Clin Oncol 2004;22:4893-900) involved 68 patients and was stopped early with one year cure rate results of 19% versus 32% in the oxygen and control arms respectively.
- 10.5 The Committee noted that clodronate is an alkylbisphosphonate and has been discontinued in New Zealand. The Committee noted that it was previously indicated for: (i) the treatment of osteolysis due to bone metastases from breast carcinomas or as a result of multiple myeloma and hypercalcaemia; (ii) hypercalcaemia as a result of extensive bone metastases or malignant bone destruction.
- 10.6 The Committee considered that the evidence supporting the use of clodronate as a treatment for osteoradionecrosis is weak with only two non-experimental cohort studies available. The first cohort study (Delanian et al. Head and Neck 2004; 27: 14) involved 18 patients with lesions where all had pre-treatment therapy with two to four weeks of antibiotics, antifungals and methylprednisolone followed by a treatment regimen of pentoxifylline and vitamin E with or without clodronate. After six months, 60% of patients in the non-clodronate group responded to treatment versus 62.5% in the clodronate group. The Committee noted that clodronate treatment was not randomly allocated and the assessors were not blinded to the treatment.
- 10.7 The Committee noted that the second cohort study (Delanian et al. Int J Radiation oncology Biol Phys 2010 Jul 15. [epub ahead of print]) describes a cohort of 54 patients who received prednisolone, amoxicillin clavulanate, ciprofloxacin and fluconazole as pre-treatment followed by treatment with pentoxifylline, vitamin E, prednisolone, ciprofloxacin and clodronate. A total of 82.5% (46/54) patients were reported as receiving treatment at six months and 43.5% of them were cited as having completely recovered. The Committee considered that there is currently no comparative evidence for the effectiveness of clodronate and the results from the second cohort study are confounded by the other treatments being given.
- 10.8 The Committee considered that there was no evidence of health benefit from clodronate provided by the applicant or in any other literature it reviewed. The Committee noted that there is also a non-experimental case report (Crepin Eur J Clin Pharmacol 2010; 66: 547-54) which indicates that there could be a risk that clodronate itself could cause osteonecrosis of the jaw.
- 10.9 The Committee considered that the authors of the clodronate studies did not provide a rationale for the use of clodronate rather than one of the other alkylbisphosphonates, noting that etidronate (also an alkylbisphosphonate) is fully funded in the Pharmaceutical Schedule.

11 Docetaxel for metastatic castration resistant prostate cancer

Application

- 11.1 The Committee reviewed an application from a clinician for the widening of funding for docetaxel on the Pharmaceutical Schedule to include treatment of patients with metastatic castration resistant prostate cancer (mCRPC).

Recommendation

- 11.2 The Committee **recommended** that funding for docetaxel on the Pharmaceutical Schedule should be widened to include the treatment of patients with mCRPC. Members gave this recommendation a low priority; however, members considered that the priority would increase if future pricing of docetaxel was similar to mitoxantrone pricing.
- 11.3 The Committee further **recommended** that its minute be provided to CaTSoP for comment.

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.*

Discussion

- 11.4 The Committee noted that approximately 3000 men per year present with prostate cancer, of whom 10-20% present with metastatic disease and in many others metastases will develop despite treatment with surgery or radiotherapy. Current treatments for metastatic prostate cancer include removing the supply of androgens, either by orchidectomy or through the use of GnRH analogues and antiandrogens (androgen ablation/castration). Members noted some prostate cancers become refractory to castration and in such cases medical treatment options were limited to mitoxantrone with prednisone or further hormonal manipulation, however, these treatments have no proven survival benefit. Members noted that radiation therapy or radioactive strontium implants may also be used in these patients.
- 11.5 The Committee noted that docetaxel, a taxane similar to paclitaxel, is currently funded for patients with various metastatic cancers, including breast, ovarian, and lung, and for patients with early breast cancer when given in combination with trastuzumab.
- 11.6 The Committee reviewed evidence for docetaxel in mCRPC from a number of studies and a meta-analysis. Key evidence comprised a large randomised, open label, phase III study, TAX 327 (Tannock et al NEJM 2004 7; 351(15):1502-12 and Berthold et al J Clin Oncol. 2008 10;26(2):242-5), in which 1006 men with metastatic hormone refractory prostate cancer received 5 mg prednisone twice daily and were randomised to receive mitoxantrone (12 mg/m² every three weeks (MP)) or docetaxel (75 mg/m² every three weeks (D3P) or 30 mg/m² weekly for five weeks of a six weekly cycle (D1P)).
- 11.7 The Committee noted that 20% of patients who received MP went on to receive docetaxel and approximately a quarter of patients who received docetaxel received

subsequent MP. Members noted that after a median follow-up of 3.5 years median overall survival in the patients receiving three weekly docetaxel was 2.9 months longer than MP treated patients (19.2 months (D3P) vs. 16.3 months (MP)) and 1.3 months longer than for the weekly docetaxel patients (17.8 months (D1P)). Members noted that prostate specific antigen (PSA) responses were improved in both docetaxel groups compared with MP but median duration of PSA response was not different. Members further noted that quality of life was significantly improved in both docetaxel groups compared with MP treated patients and a reduction in pain was more frequent in the three weekly docetaxel patients, but not the weekly docetaxel patients. The median duration of reduced pain did not differ significantly between the three groups. Members noted that docetaxel treatment was associated with significant toxicity, most notably increased risk of grade 3/4 neutropaenia and febrile neutropaenia.

- 11.8 The Committee considered that the TAX 327 study was of medium strength and quality, noting the lack of blinding may have led to potential bias and there were significant numbers of patients who crossed over.
- 11.9 The Committee also considered a Cochrane review of chemotherapy for hormone refractory prostate cancer. Members noted that the review, which included 6929 patients across a 47 phase II and III studies, concluded that evidence from randomised studies, in particular those using docetaxel, provide encouraging improvements in overall survival, palliation of symptoms and improvements in quality of life.
- 11.10 The Committee considered that overall docetaxel treatment was associated with modest survival benefits (approximately two months) compared with mitoxantrone but was significantly more costly (docetaxel is currently approximately 20 times more expensive than mitoxantrone). However, members noted that docetaxel is currently funded for metastatic lung cancer where the magnitude of benefit of treatment was similar and no other currently funded treatments for mCRPC had demonstrated any survival benefit. Members considered that if funded for mCRPC the number of patients accessing docetaxel treatment would be limited, approximately 30 patients per year.
- 11.11 The Committee noted that the price of docetaxel was likely to reduce significantly through the current 2010/11 Tender and considered that if the Special Authority was removed from docetaxel completely a number of prostate cancer patients may access docetaxel treatment earlier prior to hormone treatment.

12 Nilotinib (Tasigna) for chronic myeloid leukaemia

Application

- 12.1 The Committee reviewed an application from Novartis (NZ) Ltd for the listing of nilotinib (Tasigna) on the Pharmaceutical Schedule for the second line treatment of patients with chronic myeloid leukaemia (CML) resistant or intolerant to imatinib. The Committee also considered further information from PHARMAC staff regarding the use of nilotinib and dasatinib for the first line treatment of patients with CML.

Recommendation

- 12.2 The Committee **recommended** that nilotinib be listed in the Pharmaceutical Schedule for the treatment of patients with chronic myeloid leukaemia with a medium priority.

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.*

Discussion

- 12.3 The Committee noted that it and its Cancer Subcommittee (CaTSoP) had previously considered the funding of nilotinib in the second-line and third-line settings following treatment with imatinib or imatinib and dasatinib respectively. The Committee noted that at its May 2008 and February 2009 meetings, it had recommended that the funding of nilotinib in the second-line setting be declined due to its limited, short term data and high cost. The Committee also noted that at its November 2009 meeting, it had also recommended that the funding of nilotinib in the third-line setting also be declined. The Committee noted that dasatinib was funded for all CML patients from 1 August 2009.
- 12.4 The Committee considered longer term follow-up (24 months) safety and efficacy data from study CAM2010, the single arm phase II registration study of 400 mg b.i.d nilotinib in patients with chronic phase CML resistant or intolerant to imatinib (Kantarjian et al Blood 2010). Members also considered evidence from two randomised controlled trials (RCT) studies comparing dasatinib or nilotinib with imatinib for the first line treatment of patients with CML. The Committee considered that the evidence from these two RCTs were of high quality.
- 12.5 The Committee noted that the first RCT (Kantarjian et al. N Engl J Med 2010; 362: 2260-7) compared dasatinib (100 mg/day) with imatinib (400mg/day) in 519 patients with CML who had previously received no other treatment but anagrelide or hydroxyurea. The Committee considered that the primary outcome of complete cytogenetic response at 12 months with no Philadelphia positive metaphases on bone marrow examination was present in 76.8% of patients receiving dasatinib and 66.1% of patients receiving imatinib, $p=0.007$. The Committee noted that overall survival was 97% versus 99% in the dasatinib and imatinib arms respectively. The adverse events for dasatinib and imatinib were different as dasatinib was associated with more neutropenia, less fluid retention and imatinib was associated with more gastrointestinal side-effects although diarrhoea was equally common. The Committee noted that one weakness of this study was the open-label design which could have affected the reporting of more subjective adverse events.
- 12.6 The Committee noted the second RCT (Saglio et al. N Engl J Med 2010; 362: 2251-9) involved 846 patients who were randomised to one of three treatment arms; nilotinib 600mg/day, nilotinib 800mg/day or imatinib 400mg/day with an option to increase the dose to 800mg/day for suboptimal response or treatment failure. Patients recruited could have received anagrelide or hydroxyurea or less than two weeks of imatinib. The Committee noted that treatment discontinuation due to adverse effects occurred at similar rates in the three treatment arms. The complete cytogenetic response at 12 months was present in 80.1% of the 600mg/day nilotinib arm, 77.9% of the 800mg/day nilotinib arm and 65.0% of the imatinib arm. The Committee noted that for the primary

outcome of major molecular response, it was present in 44% of the 600mg/day nilotinib arm, 43% of the 800mg/day nilotinib arm and 22% of the imatinib arm. The Committee also noted that the adverse effect profile was different for both drugs as nilotinib was associated with more cytopenia and imatinib with more nausea and diarrhoea. The Committee noted that the weaknesses of this study included the open-label design, poor reporting of patient characteristics and it was not clear why the two doses of nilotinib were used.

- 12.7 The Committee considered a non-experimental cohort study (Kantarjian et al. Blood 2011; Jan 27; 117(4): 1141-5) where patients with imatinib intolerance or resistance were treated with 800mg/day nilotinib. For patients with at least 24 months follow up, 44% had a complete cytogenetic response. The Committee noted that progression free survival at 24 months was 64% and overall survival was 87%.
- 12.8 The Committee noted that there are no trials directly comparing nilotinib to dasatinib but the two RCTs available for these treatments versus imatinib suggests that based on the surrogate marker of complete cytogenetic response, the effect of nilotinib is similar to dasatinib. Members considered that since complete cytogenetic response is a surrogate marker for other important outcomes like progression and death, if dasatinib and nilotinib are more effective than imatinib then overall survival and freedom from transformation to advanced disease would likely be greater than 86% and 93% respectively based on the reported 7-year outcomes for the IRIS study of imatinib (O'Brien et al. Blood 2008; 112 Abstract 186).
- 12.9 The Committee considered that nilotinib seemed to have relatively less cytopaenia than dasatinib although the absolute rates were different in the two RCTs. Fluid retention was less for both nilotinib and dasatinib versus imatinib. The Committee also considered that abnormal liver function seemed to be more common with nilotinib.
- 12.10 The Committee considered that based on the two RCTs and the cohort study, patients with CML could potentially benefit from nilotinib treatment in the first or second-line settings. However, the subgroup currently most-likely to benefit from nilotinib therapy would be those intolerant or who have failed to achieve response with imatinib i.e using it in the second-line setting (estimated to be between 15 and 20% of those receiving imatinib in clinical trials).
- 12.11 The Committee considered that there is no evidence from the RCT (Saglio et al. N Engl J Med 2010; 362: 2251-9) that the 800mg/day nilotinib dose was superior to the 600mg/day dose in the first-line setting so clinicians may prefer the lower dose. The Committee considered that clinicians would potentially favour the 800mg/day nilotinib dose in the second-line setting as it was the dose used in a cohort study (Kantarjian et al. Blood 2011; Jan 27; 117(4): 1141-5). The Committee considered that clinicians would possibly use nilotinib and dasatinib in the first-line setting instead of imatinib due to the better outcomes seen in clinical trials if there was no restriction to their access. This would also depend on clinician familiarity and the different adverse reaction profiles.
- 12.12 [withheld under s9(2)(b)(ii), s9(2)(ba)(i) and/or s9(2)(j) of the OIA]